Symptoms, Function and Quality of Life in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: An Australian Based, Cross-Sectional Study.

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This research thesis is submitted in partial fulfilment of the requirements of the Bachelor of Nursing with Honours School of Nursing & Midwifery,
University of Tasmania

December 2019

Declaration of originality

"This thesis contains no material which has been accepted for a degree or diploma by the University or any other institution, except by way of background information and duly acknowledged in the thesis, and to the best of my knowledge and belief no material previously published or written by another person except where due acknowledgement is made in the text of the thesis, nor does the thesis contain any material that infringes copyright."

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Abstract

Background: Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a complex condition associated with multiple symptoms, everyday functional impairment and reduced quality of life. However, there is a paucity of published literature on the symptoms associated with everyday functional impairment and quality of life of adults in Australia with ME/CFS. In particular, use of psychometrically tested, disease specific measurement tools is limited. This has implications for understanding the unique symptom presentation of ME/CFS and appropriate clinical management.

Aim: To explore the association between symptoms, everyday function and quality of life in a cohort of adult Australians with ME/CFS.

Objectives: 1) To describe participants demographic characteristics 2) To explore symptoms (using the ME/CFS specific DePaul Symptom Questionnaire (DSQv1) and their association with everyday function and quality of life (using the generic Medical Outcomes 36-item Short Form Health Survey (SF-36) in adults who meet the Institute of Medicine clinical diagnostic criteria for ME/CFS.

Method: A cross-sectional sample was obtained from respondents to advertisements on social media, support organisation websites and newsletters. Descriptive statistics were obtained on demographics, symptom scores and everyday function and quality of life. Symptom domains were created from the DSQv1. Associations between symptom domains, everyday function and quality of life were examined using Spearman's correlations.

Results: One hundred and fifty-six respondents met the Institute of Medicines clinical diagnostic criteria. The majority of respondents were female (88.5%) and highly educated. In all, 51 (32.7%) were in paid employment and 105 (67.3%) were not in paid employment. All symptom domains had a significant, negative association with the Physical Component Summary of the SF-36 at the $p = 0.01$ level. The symptom domains with the strongest negative association were post-exertional malaise (Rs = -.596), fatigue (Rs -.539) and pain (Rs = -.506).

Conclusion: This Australian study found that post-exertional malaise, fatigue and pain have a strong negative association with everyday function and quality of life in adults with ME/CFS. These findings support local and international literature on the importance of multi-symptomatic management of ME/CFS. It also supports investigating the everyday functional limitations of patients and how they perceive their QoL to develop better measurement tools

and instigate appropriate supports. Due to the high levels of unemployment in this study, the health economic implications of ME/CFS are of high priority for further study.

Acknowledgements

I would like to thank my supervisors for their support and guidance. Dr Cynthia Honan for having me participate in the recruitment for your study and analysis of a portion of the data. Dr Jane O'Brien, for your guidance, support and steering me back on track. You have both taught me so much. I would like to acknowledge those who helped with editing certain aspects of the thesis, Emma, Mike and Jo. My husband, Michael, who encouraged me with coffee and chocolate and patience, a necessary quality of any partner of someone on a steep learning curve.

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List of terms and abbreviations

ME	Myalgic Encephalomyelitis, an earlier term often combined with Chronic Fatigue Syndrome
CFS	Chronic Fatigue Syndrome, a term developed by the Centers for Disease Control
ME/CFS	Myalgic encephalomyelitis/Chronic Fatigue Syndrome. Acronym chosen for the thesis both for brevity and reflective of current usage..
pwME	People with Myalgic Encephalomyelitis/Chronic fatigue syndrome. Standard abbreviation in the psychology literature to refer to people with a particular condition, for example with people with Multiple Sclerosis (pwMS).
Fukuda	Diagnostic criteria developed by the Centres for Disease Control
CCC	Canadian Consensus Criteria 2003 developed by expert consensus
ICC	International Consensus Criteria 2011, further extension of the CCC
IOM criteria	The most recent criteria developed by the Institute of Medicine after an extensive literature review. Also called "systemic exertion intolerance disease" originally although this name has not gained traction
DSQv1	Version one of the DePaul Symptom Questionnaire
SF-36	Medical Outcomes 36-item Short Form Health Survey
PCS	Physical Component Summary of the SF-36
MCS	Mental Component Summary of the SF-36
PEM	Post-Exertional Malaise, symptom related to physiological abnormalities of normal exertion and varies between pwME. A disease specific symptom.
Function	Used by the World Health Organisation to refer to body functions, body structures, activities and participation in the context in which the person lives.
Psychometric	The psychometric properties of a measurement instrument refer to how reliable and valid the instrument is in measuring what it sets out to measure e.g fatigue, mental health, physical function
QoL	Quality of Life. How people feel about their health condition or its consequences; hence it is a construct of "subjective well-being"
CPET	Cardio Pulmonary Exercise Test

Chapter 1 Introduction

1.1 Overview

Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome (ME/CFS) is a complex, multi-symptomatic condition that involves multiple body systems (McGregor et al. 2019). A diagnosis of ME/CFS according to the recent Institute of Medicine (IOM) clinical criteria includes "a substantial reduction or impairment in the ability to engage in pre-illness levels of occupational, educational, social or personal activities" (Institute of Medicine (IOM), 2015, p6). Hence, ME/CFS is associated with significant reductions in everyday function. Furthermore, ME/CFS is often associated with a low quality of life (QoL) (Hvidberg et al. 2015; Kingdon et al. 2018). This can be defined as how someone feels about their health condition or its consequences and is thus a "subjective perception of wellbeing" (World Health Organisation (WHO), 2007, p. 267). Use of psychometrically tested self-report questionnaires to assess how someone perceives various aspects of their health (such as physical and psychological function) is thus a useful measure of individual health outcomes (Ware and Sherborne, 1992). Moreover, this approach has been shown to reliably complement commonly used clinical data in practice (Hahn et al. 2007). On a broader policy level, such assessments allow for better evaluation of current services, allocation of funding and service design (Hand, 2016).

Despite ME/CFS being a multi-symptomatic condition, there is a paucity of literature on the symptoms most associated with poor everyday function and QoL within the Australian population using psychometrically tested assessment tools. This is important because people with ME/CFS (pwME) often report problems with obtaining a diagnosis, negative health care encounters, and stigma relating to the severity of their reported symptoms or reductions in everyday function (Anderson et al. 2012; McManimen et al. 2018). Although the literature that has identified these factors is largely international, these problems are evident within the Australian health care system. A recent report to the Chief Executive Officer of the National Health and Medical Research Council (National Health and Medical Research Council (NHMRC) 2019) highlighted the difficulty people pwME have in Australia accessing government administered support or appropriate health care. In the public consultation for the report, patients, researchers and health care providers identified delays in diagnosis, stigma and inappropriate symptom management experienced by patients as significant issues. Hence increasing the knowledge base regarding the association between symptoms and everyday function may improve health care for pwME by 1) increasing health care practitioners

knowledge of the symptoms most in need of management and 2) fostering understanding of the significant reductions in everyday function and QoL (Friedman et al. 2019).

1.2 Research question

The original working question was “Is there one symptom that has the strongest association with everyday functional impairment and QoL in ME/CFS”. For example, fatigue is a symptom that has strong associations with ME/CFS. However, after a review of the literature it was clear that there are many symptoms that may be associated with reduction in everyday function and QoL hence the final question was:

“Which symptoms are associated with everyday functional impairment and reduced QoL in ME/CFS?”.

In addition to answering the specific research question, the demographic characteristics of the participants is explored in order to understand the specific ME/CFS population captured such as gender distribution, education and employment.

1.3 Data

The data for this thesis comes from a larger research project on ME/CFS. The process for this thesis involved two elements: 1) assisting with recruitment for the larger study 2) formulation of a research question from the literature review to apply to a portion of that data and 3) analysis of data.

Chapter 2 Literature review

2.1 Introduction

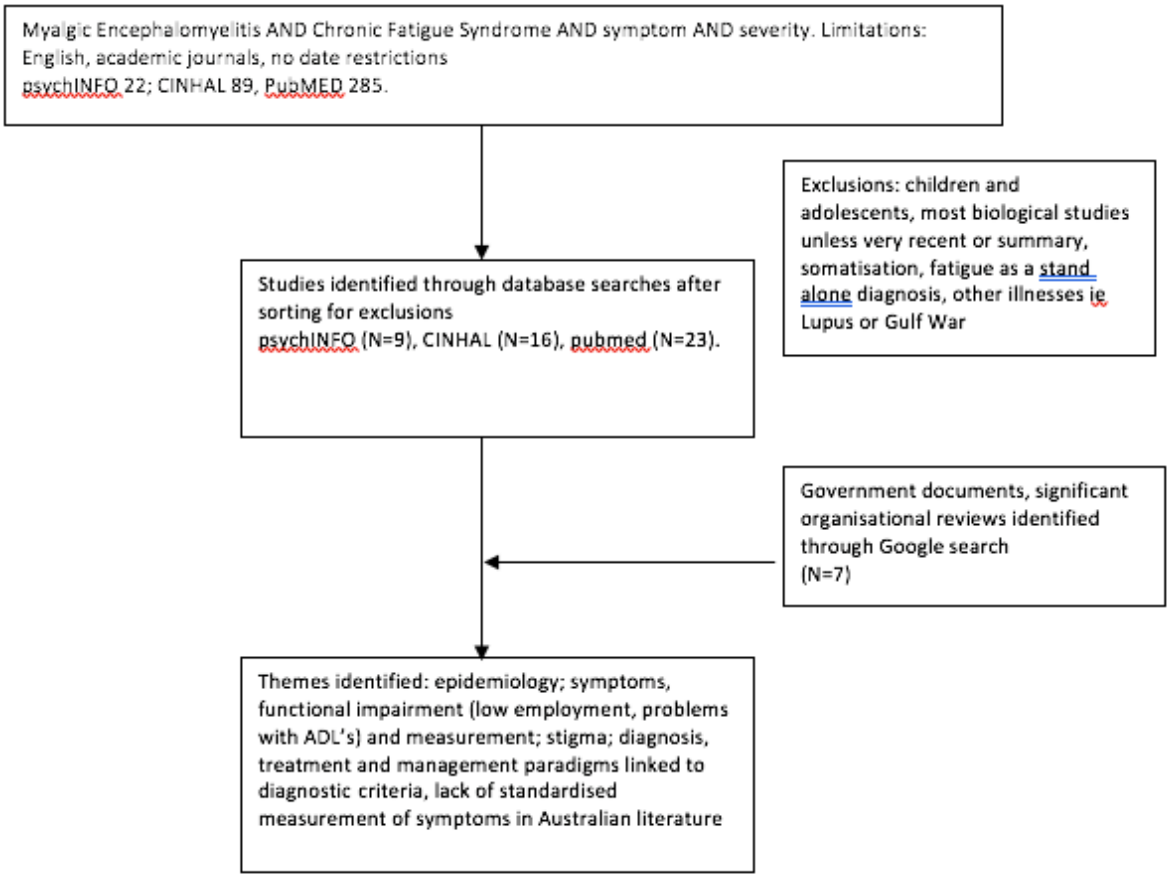
There is currently no consensus on the diagnostic criteria to apply to a patient presenting with symptoms of ME/CFS in clinical practice or to apply within a research setting (IOM, 2015). One systematic review counted twenty proposed criteria (Brurberg et al. 2014) with a further simplified clinical diagnostic criteria introduced by the IOM in 2015 (IOM, 2015). This situation is compounded by the lack of a clinically acceptable diagnostic biomarker (Vanelzakker, Brumfield & Lara Mejia 2019). Furthermore, ME/CFS can present in different ways. There are documented epidemics however cases are thought to be largely sporadic (Jason et al. 2009a). Symptom presentation may be either rapid or gradual with ongoing, shifting symptom patterns (Daniel, Annesley & Fisher 2019). This situation complicates research endeavours as it is difficult to compare studies with such heterogenous patient cohorts (IOM, 2015). It has also contributed to confusion for health care workers in making an accurate diagnosis (NHMRC, 2019). Currently diagnosis relies on identification of core features such as a significant reduction in pre illness level of capacity and self-reported symptoms. These symptoms vary according to diagnostic criteria but usually include profound fatigue, cognitive impairment, pain and difficulty with sleep. Specific to ME/CFS, there is often a delayed exacerbation of symptoms and protracted recovery to baseline after physical, cognitive or emotional exertion, termed post-exertional malaise (PEM) (Davenport et al. 2019).

Measurement of reported symptoms in the literature has been inconsistent and therefore it can be difficult to compare studies or develop treatment approaches. Hence, after briefly discussing the search strategy used to identify the relevant literature, this chapter will begin with an overview of the epidemiology of ME/CFS and some of the associated functional limitations associated with the condition. The different approaches to symptoms and their management will then be examined via a review of diagnostic criteria and subsequent treatment modalities currently offered to patients and the evidence attached to these modalities. An examination of two self-report tools to accurately measure symptoms (the DSQv1) and everyday function and QoL (SF-36) will be made. A gap in the Australian literature that examines the relationship between ME/CFS specific symptoms, functional limitations and QoL using these two questionnaires is identified.

2.2 Search strategy

A search of the literature was conducted to identify studies investigating symptoms, measurement of symptoms and symptom severity. Searches were conducted in PubMed, CINHAL, and PsychINFO using the terms ‘Myalgic Encephalomyelitis’, ‘Chronic Fatigue Syndrome’, AND ‘severity’ AND ‘symptoms’ with an additional search on Google to identify government reports. The number of articles identified and themes that were identified are outlined in Figure 1. From these searches an initial matrix was developed (Appendix 1). The matrix is not an exhaustive document of all literature referenced however it formed the basis from which the literature review developed. Primary sources included both peer reviewed qualitative and quantitative research; studies on biological causes were included if they converged with identified themes. Secondary sources included significant government reviews and systematic reviews based on primary sources. The focus of this review is on adults as there are epidemiological, contextual and phenotypic differences between children and adults with ME/CFS (Rowe et al. 2017). It was noted that many studies of ME/CFS have not been replicated, hence no date range was specified, and some referenced articles are more than ten years old. Articles were limited to English. As themes emerged, an iterative process was employed to develop a coherent understanding of the topic and identify further areas for knowledge development.

Figure 1 Literature search flow chart



2.3 Epidemiology

Reported prevalence estimates of ME/CFS vary widely and range from 0.03% to 6.41% (Carruthers et al. 2012; Lloyd et al. 1990; Nacul et al. 2011). Higher prevalence estimates occur with self-report data compared to clinically confirmed cases (Johnston et al. 2013) or with use of broad diagnostic criteria which may include people with unspecified fatigue, as opposed to ME/CFS (Baraniuk 2017; Jason et al. 2009b). This highlights one of the inconsistencies in the literature and challenges for identifying similar cohorts for biologic research or needs assessment and service design. The only Australian point prevalence study (Lloyd et al. 1990) found a low prevalence of 0.03% across a broad demographic population using case identification criteria developed by the researchers rather than an international standard. By contrast a meta-analysis (Johnston et al. 2013) found an international pooled prevalence of 0.87% (95% CI: 0.23-1.29) based on clinically assessed samples. The meta-analysis was of cases according to a criterion developed by the Centers for Disease Control, the Fukuda criteria (Fukuda et el. 1994) which has been the most utilised criteria (IOM, 2015). This estimate needs to be interpreted with caution as there are indications ME/CFS is underdiagnosed with community based population studies suggesting up to 90% of people with pwME may not be diagnosed (Jason et al. 1999; Reyes et al. 2003). Although true population prevalence studies are approximately twenty years old more recent qualitative studies indicate general practitioners are often unwilling to make a diagnosis (Bayliss et al. 2014) suggesting rates of diagnosis may remain low.

The reported ratio of males to females with ME/CFS in the literature is generally 1:4 (IOM 2015). However a recent study in the United States using large scale medical claims data found 40% of those diagnosed were men (Valdez et al. 2019). It is not clear what is causing this discrepancy but one possible explanation is that the large scale data mining techniques used by Valdez et al. (2019) were able to capture a better estimate of prevalence in men and women. This requires further investigation as it is in contrast to a large community-based population prevalence study by Jason et al. (1999, p. 2135) where 522 women and 291 men were affected per 100 000. ME/CFS can occur at any age however two peaks for age of onset have been described; one from 10 -19 years (Bakken et al. 2014) and the second between 25 – 35 years of age (Jason et al. 1999) thus affecting people at critical educational and employment periods of their lives (Collin et al. 2011; Rowe et al. 2017).

2.4 Everyday functional impairment

Despite the known significant reduction in everyday function, there is no agreed severity tool for clinicians to determine this assessment (Hardcastle et al. 2016; Strassheim et al. 2017). According to one clinical primer which provides information for clinicians managing pwME (Carruthers et al. 2012), a person with mild ME/CFS will likely remain employed and manage Activities of Daily Living (ADLs) with difficulty. A person with moderate ME/CFS will have a 50% reduction in activity, restricted mobility and be unable to consistently perform ADLs such as cleaning or daily bathing. A person with severe ME/CFS is housebound and only able to attend minimal ADLs and will likely require mobility aids and a very severe case is dependent on a carer for all functions and may be unable to hold a conversation. In a scoping review on severe and very severe ME/CFS, Strassheim et al. (2017) found the prevalence of this category of patients to be quoted as ten to twenty five percent by patient organisations. However, the true prevalence has not been established due to differences in assessment of severity and difficulties accessing this group of pwME due to the severity of their condition.

Currently it is thought that recovery from ME/CFS is low and definitions of recovery are inconsistent (IOM, 2015). Of particular importance, self-reports of recovery appear to be unreliable. Brown et al. (2012) reviewed 25 pwME who had been diagnosed approximately 25 years previously and found 17 out 23 outcomes were not statistically different between those who classified themselves as recovered compared to those who reported still having ME/CFS. This was a small study however a more recent observational cohort study (n=784) also examined symptoms and function experienced by young adults who had been diagnosed in adolescence. The study found considerable crossover in functional scores between those who defined themselves as recovered and those who did not (Rowe 2019). In a nine-year longitudinal study, only two out of 34 participants had recovered; the highest indicator of functional impairment (defined as disability) was work status followed by the symptom PEM (Andersen, Permin & Albrecht 2008).

Indeed, one area that exemplifies reduction in function in ME/CFS is work capacity and retention (Schafer et al. 2015). An Australian cross-sectional study found 34.2% on a disability pension, 26% as unemployed and only 9.7% maintained full time employment. The study did not identify if there were particular symptoms with a stronger association with reduced work activity (Johnston, Staines & Marshall-Gradisnik 2016). This was explored in a

large Spanish community based prospective study (n=1086) (Castro-Marrero et al. 2019) where they found the symptoms most associated with unemployment were broad and related to muscular, cognitive, neurological, autonomic and immune systems. However in their regression model, only autonomic related symptoms predicted work disability. The study did not report on return to work rates and a critical review of the literature found that it was not possible to provide definitive data on this due to heterogeneity of studies. However the indication is return to work rates are low and successful maintenance of employment relies on flexible arrangements with lower work hours (Vink & Vink-Niese 2019).
Qualitative literature not only identifies reductions in function but explores the difficulties pwME have in adapting to their limitations. Most notably, there are issues related to the health care encounter that may create barriers to better function and QoL. Anderson, Jason and Hlavaty (2014) interviewed 19 participants from a larger community based epidemiological study and found restructuring of life was required in order to cope with the impairments associated with the onset of ME/CFS. Participants identified limited medical, social or structural support as factors contributing to difficulties with adjusting to changes in circumstances. Likewise, a study of 26 adults with Post Viral Fatigue Syndrome, a term which has been equated with ME/CFS, found participants experienced delays in medical diagnosis, lack of understanding from health care professionals regarding the impact symptoms were having on everyday life and resulting lack of symptomatic management (Stormorken, Jason & Kirkevold 2017). It must be noted that both studies (Anderson, Jason & Hlavaty 2014; Stormorken, Jason & Kirkevold 2017) rely on recall hence recall bias may be a factor in how experiences are interpreted over time and further prospective studies are warranted.

2.5 ME/CFS and stigma

Experience of stigma is a common theme within the literature and often relates to how symptoms are interpreted by others and how they are experienced by pwME. A large cross-sectional study (n=551) found evidence of a relationship between higher ME/CFS symptom severity, experience of stigma and suicidal ideation, both with and without depression in adults with ME/CFS (McManimen et al. 2018). One source of stigma sits within the individual and structural components of the health care system. A qualitative meta synthesis found some general practitioners and practice nurses framed patients as difficult or exaggerating the impact of their symptoms (Bayliss et al. 2014). One explanation for this

could be that clinicians identify a lack of confidence in managing ME/CFS symptoms due to the complexity and controversy over diagnosis and lack of available education or management pathways (Anderson et al. 2012; Bayliss et al. 2016). A further contributing factor may lie in differences in interpretation of the meaning of symptoms between schools of thought and, at times, between patients and health care providers (Bayliss et al. 2014; Chew-Graham et al. 2011). Hence, development of resources for health care workers requires an understanding of the historical and current criteria available to diagnose ME/CFS as these exemplify some of the different interpretations attached to presenting symptoms.

2.6 Historical and current perspectives on diagnosing ME/CFS

2.6.1 Context for multiple criteria.

Shifting perceptions and narratives surrounding ME/CFS can be seen in the diagnostic criteria that have emerged with different groups developing diagnostic criteria that reflect particular interpretations of the literature, including interpretation of prevailing biological findings and patient reports of symptoms (Geraghty & Esmail 2016).

2.6.2 Oxford Criteria

A behavioural interpretation of presenting symptoms was developed in the 1970's when a group of psychiatrists (McEvedy and Beard, 1970) reviewed the Royal Free epidemic of 1955, and concluded that these cases were the product of hysteria due to cases being predominantly women with no evidence of objective findings (IOM, 2015; McEvedy and Beard, 1970). In the late 1990's a group of British psychiatrists (Vercoulen et al., 1998) introduced a slightly different model where any ongoing biological aberrations were interpreted as consequences of perpetuating, false or maladaptive beliefs and behaviours regarding symptoms (Maes and Twisk, 2010, Sunnquist and Jason, 2018). In this model, pwME are encouraged to push through perceived negative symptoms in an attempt to re-train the body towards normal physiological function (Davenport et al., 2010). Associated with this model is the Oxford Criteria (Sharpe et al., 1991). This criteria requires: fatigue of six months or longer, reduction in pre illness function and exclusion of psychiatric illness (Sharpe et al., 1991). Lack of specificity is a problem with this criteria as study participants may not have ME/CFS, but other fatigue causing illnesses such as an autoimmune disease or generalised chronic fatigue of unknown origin (Baraniuk 2017). There is decreasing acceptance of this criteria for studying ME/CFS (IOM, 2015),

however studies into treatment modalities based on false belief and behaviours still influence treatment guidelines (NHMRC, 2019).

2.6.3 The problem with unspecified fatigue as a diagnosis of ME/CFS

Many of the proposed criteria for ME/CFS include the presence of fatigue as an essential criterion for diagnosis, with the required duration of fatigue usually being six months or more with additional symptoms as discussed below. Whilst fatigue is a prominent and often incapacitating symptom in ME/CFS, it is also a common symptom across many disease processes, and causes may range from acute viral infection, autoimmune disease, cancer, psychiatric illness and medication side effects (Wilson et al., 2014). Fatigue is a subjective description that is difficult to quantify in biomedical terms. Weather the fatigue experienced by pwME shares similar biological mechanisms to other illnesses with a high fatigue component is an outstanding question (Karshikoff, Sundelin & Lasselin 2017). As fatigue is difficult to define, health care professionals often struggle to understand the distinct needs of the person reporting fatigue (Gielissen et al., 2007). For this reason it is important that the language used is descriptive of the fatigue experienced within an individual condition (Jason et al. 2009b). For example, there may be separate symptoms or dimensions to fatigue that are contributing to an overall reporting of fatigue. For example, cognitive fatigue, sometimes referred as “brain fog” by pwME (Carruthers et al. 2012) may reflect issues with memory or concentration and is one of the most prevalent reported symptoms (IOM, 2015). Symptoms may also fluctuate depending on other factors such as how physically fatigued the person may be, or duration of the cognitive task (Attree et al. 2014; Carruthers et al. 2012; Jason et al. 2009c). Additionally, other symptoms may contribute to an overall perception of fatigue, that may be amenable to treatment and may consequently reduce fatigue. Jones et al. (2011) found orthostatic symptoms, anxiety and depression were independent predictors of current fatigue. Thus, attenuation of fatigue may be possible with interventions targeted to individual symptoms or circumstances that may not appear directly related to fatigue. Hence, assessment of the full spectrum of symptoms within ME/CFS is important in establishing contributors to fatigue, development of symptom appropriate management and further research into biological mechanisms.

2.6.4 The inclusion of post-exertional malaise

A recent shift towards a biological interpretation of symptoms has occurred that focuses on the unique issues with exertion and energy production in ME/CFS with the term PEM being

used to encompass these findings (Holtzman et al. 2019; McGregor et al. 2019). PEM is now seen as specific for a diagnosis of ME/CFS (IOM, 2015). PEM has been described as the increase in some or all of a persons' symptoms, such as fatigue, muscle fatigability, pain, cognitive issues, autonomic or immunological symptoms post physical, cognitive or psychological exertion that is not proportional to that exertion (Arroll et al. 2014; Chu et al. 2018; Jason et al. 2018a). Although fatigue post exertion is evident in many disease processes, such as cancer and multiple sclerosis, the exacerbation of multiple symptom domains is likely unique to ME/CFS (Jason & Sunnquist 2018a; McGregor et al. 2019). Additionally, the temporal component of PEM is unique and can involve both a delay in exacerbation of symptoms and a variable trajectory of recovery to baseline symptom severity and function (Chu et al. 2018; McGregor et al. 2019). Self-reported recovery ranges from 24 hours to months (Chu et al. 2018; Holtzman et al. 2019). Objective measurement of delayed exacerbation and recovery has also been examined using sequential, two day Cardiopulmonary Exercise Testing (CPET) whereby pwME are unable to reproduce oxygen consumption and workload levels at Ventilatory Threshold (VT) on day two indicating a post exertional reduction in exercise capacity (Snell et al. 2013). This is not evident in healthy sedentary controls or those with cardiovascular disease, lung disease, end stage renal disease and cystic fibrosis (Hodges, Nielsen & Baken 2018; Keller, Pryor & Giloteaux 2014; Snell et al. 2013). Stevens et al. (2018) further elaborates that VT is not normally reached during activities of daily living, however pwME may enter anaerobic levels of activity resulting in symptom exacerbation during minor activities. Sequential CPET has been suggested as an accurate diagnostic test (Nelson et al. 2019) although it carries high risk to pwME as it is unclear how to assess the risk posed to each individual by deliberately triggering PEM (Stevens et al. 2018).

2.6.5 Fukuda criteria, Canadian Consensus Criteria, International Consensus Criteria and the Institute of Medicine clinical criteria

Table 1 sets out the essential and optional symptoms for a diagnosis according to the Fukuda criteria (Fukuda et al. 1994), Canadian Consensus Criteria (CCC) (Carruthers et al. 2003), International Consensus Criteria (ICC) (Carruthers et al. 2011) and the Institute of Medicine clinical criteria (IOM, 2015). A recent review (Blomberg et al. 2018) found more coherent pathophysiological findings are evident in studies applying these criteria and, except for the Fukuda criteria, PEM is an essential symptom. A number of studies have also found that the

CCC and ICC select smaller cohorts with more functional impairment and severe symptoms, suggesting specificity (Jason et al. 2016). Although this may have utility in identifying biological causation, these criteria may miss those pwME who are less severe in clinical contexts and they may be too complex to apply within a standard clinical encounter (IOM, 2015). The IOM clinical criteria is a simplified criteria for use in a clinical setting and captures a wider range of severity (Jason, Sunnquist et al. 2015a). Jason et al (2015b) found including orthostatic intolerance in the IOM criteria only increased the percentage of those meeting the criteria by two percent. However in terms of clinical utility, orthostatic intolerance may be underdiagnosed and it is a symptom amenable to treatment (Reynolds et al. 2014). On the other hand, the criteria omits pain, which is a prevalent symptom in ME/CFS (Strand et al. 2019). It will remain unclear if these criteria represent distinct clinical entities (Twisk 2019) or related subgroups until biological markers are discovered (Daniel, Annesley & Fisher 2019). However, the IOM report emphasised that ME/CFS is a diagnosis to be made with their simplified diagnostic criteria providing an easy screening tool to use in clinical settings (IOM 2015).

Table 1. Symptoms according to diagnostic criteria

Fukuda CFS 1994 (Fukuda et al. 1994)	Canadian Consensus Criteria ME/CFS 2003 (Carruthers et al. 2003)	International Consensus Criteria ME 2011 (Carruthers et al. 2011)	Institute of Medicine (Institute of Medicine (IOM) 2015)
• Prolonged or chronic fatigue that persists or relapses for six months or more AND • Four or more of the following - Impaired memory or concentration - Sore throat - Tender cervical or axillary lymph nodes - Muscle pain - Multi-joint pain - New headaches - Post-exertional malaise	• Illness lasting six or more months • Fatigue • Post-exertional malaise • Sleep dysfunction • Pain • Two or more neurological/cognitive manifestations AND • At least one from two of the following categories - Autonomic - Neuroendocrine - Immune	• Post-exertional neuroimmune exhaustion • At least one symptom from three of the following categories - Neurocognitive - Pain - Sleep disturbance - Neurosensory, perceptual or motor disturbances AND • At least one symptom from three of the following - Flu like symptoms - Susceptibility to viral infections with prolonged recovery periods - Gastrointestinal tract - Genitourinary - Food sensitivities AND • At least one symptom from the following - Cardiovascular - Respiratory - Loss of thermostatic stability - Intolerance of extremes of temperature	• Symptoms, including fatigue that is not lifelong, not the result of excessive exertion and not substantially alleviated by rest have persisted for more than six months AND • Post exertional malaise • Unrefreshing sleep AND • At least one of the two symptoms - Cognitive impairment - Orthostatic intolerance

2.7 Symptom management and treatment options

2.7.1 Pharmacological treatment

A number of pharmacological treatments have been explored but have failed at more advanced phase trials. A recent example is a randomised double-blind placebo-controlled phase three trial of the B-Lymphocyte depletion drug Rituximab in those with a CCC diagnosis (Fluge et al. 2019). The trial found no statistically significant difference between cases and controls. This was in contrast to a promising phase two trial of the same drug (Fluge et al. 2011). A systematic review of pharmacological therapies for ME/CFS found that there was inconsistent evidence for any of the therapies assessed (Collatz et al. 2016). The review found two major weaknesses in the literature to be lack of standardisation of participants according to diagnostic criteria and outcome measures. Hence, pharmacological and nutraceutical treatments are currently prescribed based on clinician experience to target individual symptoms (Bested & Marshall 2015; Carruthers et al. 2012; Castro-Marrero et al. 2017; Smith et al. 2014).

2.7.2 Graded Exercise Therapy and Cognitive Behavioural Therapy

Graded Exercise Therapy (GET) and Cognitive Behavioural Therapy (CBT) tailored specifically to ME/CFS are treatment approaches based on the behavioural paradigm and play a significant influence on current management approaches (Vink & Vink-Niese 2018). The safety and efficacy of GET and CBT for ME/CFS have recently been questioned by a number of authors (Kindlon 2017; Sunnquist & Jason 2018; Vink & Vink-Niese 2018; Wilshire et al. 2018). Two systematic reviews found poor or little evidence for CBT and GET, especially when removing those studies utilising the Oxford criteria from analysis (Nijs et al. 2011; Smith et al. 2014). A systematic review by Castro-Marrero et al. (2017) found no evidence that these therapies increase a meaningful return to work.

2.7.3 Activity pacing

A critical review on activity management (Goudsmit et al., 2012), often termed pacing in the ME/CFS literature, found that pacing strategies that encourage pwME to stay within their available energy boundaries can assist with stabilisation and possibly reduce the severity of exertion related symptoms. A case report that appears to confirm the clinical utility of CPET testing followed one person who was instructed to only perform prescribed exercises below their anaerobic threshold, established with CPET. At one year follow up, cardiovascular and

pulmonary parameters had improved and subjective time to recovery from testing had improved by 75% (Stevens & Davenport 2010). Larger longitudinal studies following pwME who undertake sequential CPET and follow prescribed exercise parameters would be informative as the literature is unclear how much limitation pwME need to place on their activity to reduce or avoid PEM with changes in immune function found even at sub maximal exercise (Nijs et al. 2010). Additionally, only six percent out of a large cohort (n=1534) from a community based participatory research study (Holtzman et al. 2019) felt pacing completely eliminated PEM.

2.8 Australian context

Formal estimates of ME/CFS disease burden in Australia are more than ten years old. A report in 1999 (Mathers, Vos & Stevenson 1999) by the Australian Institute of Health and Welfare (AIHW) used the EQ-5D+ regression model to estimate Disability Adjusted Life Years. The EQ-5D+ is a Health Related Quality of Life instrument used extensively in cost analysis related to health which uses an anchored scale where 0 is perfect health and 1 is death (Rand-Hendriksen, Augestad & Dahl 2012). The AIHW estimated a mild handicap of 0.137, moderate 0.449 and severe or profound 0.760 for those meeting the Fukuda criteria (Mathers, Vos & Stevenson 1999). Moreover, guidelines for medical professionals were last updated in 2002 (Royal Australian College of Practitioners 2002). Significantly, changes in medical diagnostic and management guidelines have advanced internationally since publication of this guideline (IOM, 2015; NHMRC, 2019) and this review identified no published nursing or allied health guidelines.

There have been a small number of Australian based studies examining symptoms and their association with function and QoL. Lowry and Pakenham (2008) used the Fukuda criteria in a cross-sectional study of Australian participants to assess the effect of fatigue on physical and psychological wellbeing and found fatigue, mental fatigue severity, older age, and female gender to be strong predictors of physical functional issues. Although 63% of participants reported psychological distress, these had weak positive associations with physical fatigue and symptom frequency. One limitation of this study was that it did not distinguish fatigue from PEM. In a more recent study Johnston, Staines and Marshall-Gradisnik (2016) used self-report of a medical diagnosis and symptom inventories to classify respondents according to the ICC or Fukuda criteria. The study did not include a clinical interview to confirm meeting either criteria. Overall, across diagnostic criteria, the most prevalent symptoms were

fatigue, PEM, cognitive difficulties, pain, sleep, light headedness and sensory problems. However, the authors highlighted the problem with using symptom inventories without threshold scores or standardised methods for assessing reduction in function when classifying participants into diagnostic categories. Presence of a symptom alone may not be adequate to distinguish between groups with and without ME/CFS, given that many disease processes share similar symptoms. In one study, a third of controls could meet ME/CFS diagnostic criteria by symptoms alone whereas when frequency and severity thresholds were applied, the misclassification of cases dropped to 5% (Jason et al. 2014). Hence the authors (Johnston, Staines and Marshall-Gradisnik, 2016) suggest further studies utilising symptom measurement scales that use symptom threshold scores that have been rigorously tested.

2.9 Measurement of symptoms and outcomes

Different methods for symptom measurement and definition of ME/CFS have influenced interpretation of study findings in ME/CFS. For example, a large international study (n = 37 724) combined a number of studies and data sets and concluded there is an empirical 'chronic fatigue' state with a core mood component (Hickie et al. 2009). However Jason et al. (2010a) note that the factor analysis combined ME/CFS Fukuda and those with a general fatigue diagnosis rather than separating ME/CFS diagnosis and other fatigue causing illnesses, thus making it difficult to assess which participants have a core mood component to their illness. Similarly, a large prospective cohort trial (Harvey et al. 2008) established a dose response relationship between a prior psychiatric diagnosis and subsequent development of ME/CFS, which was defined as 'fatigue' or a self-reported diagnosis of ME/CFS. Although it is biologically plausible that previous exposures to stress, including psychological stress, may lead to ME/CFS (Chu et al. 2019) it remains that otherwise well powered studies have not always been specific in their definitions of ME/CFS.

Potential issues also arise in scales used to measure symptoms; some conflate fatigue that is physical or cognitive in origin, and fatigue that is related to psychological symptoms. One common scale used in ME/CFS research is the Chalder fatigue Scale (Chalder et al. 1993). The scale has strong internal consistency and is able to distinguish between people with ME/CFS and healthy controls but is not able to distinguish between people with ME/CFS and depression, lupus or multiple sclerosis (Jason et al., 2011). Additionally, as PEM is a distinct symptom construct to ME/CFS, generic scales do not capture this symptom, or they may conflate fatigue and PEM (Jason & Sunnquist 2018a).

2.9.1 The DePaul Symptom Questionnaire

The DePaul Symptom Questionnaire (DSQ) (Jason et al. 2010b) uses frequency and severity threshold symptom scores to classify ME/CFS participants who meet a number of diagnostic criteria. The first version of the questionnaire (DSQv1) developed from operationalising the CCC as the criteria was initially developed for clinical practice and not as an operationalised research definition (Jason et al. 2010b). The DSQv1 has been shown to reliably differentiate between ME/CFS, major depression and healthy controls in a research setting (Murdock et al. 2017). It has also demonstrates good content validity and test-retest reliability (Jason et al. 2015c). Recent studies that compare objective measures of autonomic (Kemp et al. 2019) and cognitive dysfunction (Zinn, Zinn & Jason 2017) have found the DSQ can adequately measure these constructs. To date the author is not aware of any published studies using the DSQ to measure symptoms in an Australian cohort.

2.9.2 Medical Outcomes Study 36-item Short-Form Health Survey

The SF-36 is a generic measure of self-perception of health status (Ware & Sherbourne 1992) and has been used consistently in studies in adults with ME/CFS (Buchwald et al. 1996; Hardt et al. 2001; Jason et al. 2017; Kingdon et al. 2018). The SF-36 provides measurement of multidimensional health concepts and disease impact on physical, psychological and social functioning domains (Ware & Sherbourne 1992) and has shown to be reliable and valid in assessing these domains (Brazier et al. 1992; McHorney, Ware & Raczek 1993). It includes two domains that specifically examine the respondents overall perception of their health, these being the General Health and Vitality (McHorney, Ware & Raczek 1993). In regards to ME/CFS, Jason et al. (2011) found the Role Physical, Social Functioning and Vitality subscales had the best sensitivity and specificity to distinguish between those with ME/CFS and those without whereas the Role Emotional performed the worst. Because the DSQv1 uses these sub scales to establish 'substantial reductions in function' (Jason & Sunnquist 2018b) and due to the widespread use of the SF-36 in the ME/CFS literature it was chosen as part of the full study this thesis draws from (See Appendix 2 for literature search of the SF-36). Some concerns have been documented in regards to the utility of this questionnaire in the ME/CFS population. For example, Davenport et al. (2011) found the physical function, body pain, general health, vitality and social domains were able to predict recovery within one day of CPET in a combined sample of sedentary controls and ME/CFS. However, when they considered group differences over one week there was no statistical

difference. The authors suggest this may be partially explained by a number of subscale scores being rated 0 by the ME/CFS participants at both time points. Furthermore, Murdock and colleagues (2017) also found possible floor effects in the Role Limitations sub-scale with 89% of patients scoring zero. The floor effects do raise concerns regarding the scales utility in any study looking to measure variance in function, change over time, or adverse effects from an intervention such as a further reduction in function. For this reason, floor and ceiling effects will be reported on in the present study if they occur.

2.10 Conclusion

This chapter identified several intersecting themes within the literature regarding accurate measurement of the ME/CFS population in regard to diagnosis, functional impairment and measurement and interpretation of symptoms. There is considerable heterogeneity of study participants due to varying methods for selecting participants for research, in regard to diagnostic criteria, study design and feasibility of accessing more severe participants. The different interpretation of symptoms, exemplified in the diagnostic criteria, emerged as a point of difference that has influenced treatment approaches. The symptom PEM emerged as disease specific; as PEM is unique it cannot be captured using generic fatigue scales. There are also outstanding questions regarding the inclusion of orthostatic intolerance in the IOM clinical criteria and the omission of pain. This leads to the aim of the present study which is to explore the relationship between symptoms and their association with everyday functional capacity and QoL using the ME/CFS specific symptom measurement tool the DSQv1, in order to extend the research base in Australia. This may identify further areas for research in relation to appropriate health care of individuals with ME/CFS.

Chapter 3 Method

3.1 Overview and study design

This chapter details the methods used in the current study and will describe the research design, data collection and management, data analysis approach and ethical considerations. Building on Chapter 2, further details are provided regarding the DSQv1 and SF-36. A cross-sectional survey design was employed for this study. Descriptive and correlation statistics were used to explore the symptoms, function, and QoL, and the relationships between them, in a cohort of Australians who met the IOM clinical diagnostic criteria. Descriptive research is a non-experimental research method used to describe and summarise data that is collected in a systematic fashion, but it does not seek to manipulate variables (Da Costa & Schneider 2016). Correlation statistics measure the extent to which two variables are related hence there is not a dependent and independent variable as causality is not being established (Pallant 2016). In the present study operationalised definitions, in the form of questionnaires, allowed for subjective experiences such as symptoms and self-perception of functional capacity and QoL to be consistently categorised and the questionnaires were completed without the researcher present. Self-report measurement of symptoms is as an important element in understanding illness experience from the patients' point of view (Haywood, Staniszewska & Chapman 2012; Valderas & Alonso 2008) that may strengthen problem identification in physical or psychosocial domains with the long term aim of improving service design (Hahn et al. 2007).

3.2 Measures:

Participants completed the following self-reported questionnaires on demographics, symptoms, function and QoL (listed below).

3.2.1 Sociodemographic data

Participant reported their: age, gender, marital status, highest level of education, language spoken at home, employment status, length of time that they had been experiencing symptoms and length of time that they had had a diagnosis.

3.2.2 ME/CFS symptoms

The DSQv1 psychometric properties have been discussed in chapter one section 2.8.1 hence this section aims to provide an explanation of how the scale works and how the symptom domains were created for the present study. The DSQv1 has a core symptom inventory of 54 items which are organised under domain headings, these being: fatigue, PEM, sleep, pain,

neurocognitive, autonomic, neuroendocrine and immune. Participants rate each symptom separately for frequency and severity on 5-point Likert-type scales: 0=‘none of the time’, 1=a little of the time, 2=about half the time, 3=most of the time, and 4=all of the time over a retrospective six month period at time of completing the questionnaire. For this study the 54 symptoms and their original grouping (Jason et al. 2010b) were used to devise composite symptom domains as in a study by Jason et al. (2017) and these were: Fatigue (one item); PEM (six items e.g., “dead heavy feeling after exercise); sleep (five items e.g., “problems with “unrefreshing sleep”); pain (seven items e.g., “muscle pain”); neurocognitive (thirteen items e.g., “Absent mindedness”); autonomic (seven items e.g., “bladder problems”); neuroendocrine (ten items e.g., “feeling hot/cold for no reason”); immune (five items e.g., “sore throat”). Scoring of the scale involved two steps: 1) individual frequency and severity scores for each symptom were multiplied by 25 and averaged together to create a composite score on a 100-point scale with higher scores indicating higher symptom severity (Jason and Sunnquist, 2018b) and 2) the domains were created by adding together then averaging the composite severity scores of items within each domain. Each domain had a possible composite score ranging from 0 to 100 with higher scores indicating higher domain severity. The DSQv1 is available on REDCap's shared library (Harris et al., 2009).

3.2.3 Everyday function and QoL

The psychometric properties of the SF-36 are discussed section 2.9.1 hence this section will further elaborate on the structure of the scale. The SF-36 comprises eight subscales: Physical Functioning (such as ability to climb stairs, running, lifting or walking); Role Physical (role limitations such as employment due to physical health problems); Bodily Pain (intensity and interference with normal activities); General Health perceptions (respondents perception of their health status); Social Functioning (impact of physical or emotional problems on social interactions and capacity); Vitality (measure of perception of energy and fatigue); Role Emotional (role limitations due to emotional problems) and Mental Health (anxiety, depression and psychological well-being). Respondents are asked to respond to each question in regard to the last month at the time of completing the questionnaire. These sub scales can be converted to two summary measures: physical component summary (PCS) and mental component summary (MCS). Responses to questions defining each SF-36 domain were combined and transformed to 100 point scales with 100 indicating better health status (Ware et al., 1994). The MCS, in addition to two specific mental health domains, includes Social

Function Vitality. The way the questions are framed for these two domains could reflect limitations due to mental or physical related issues (McHorney, Ware & Raczek 1993) hence the full eight subscales will be used to allow for a better exploration of mental and physical health.

3.2.4 Case definition

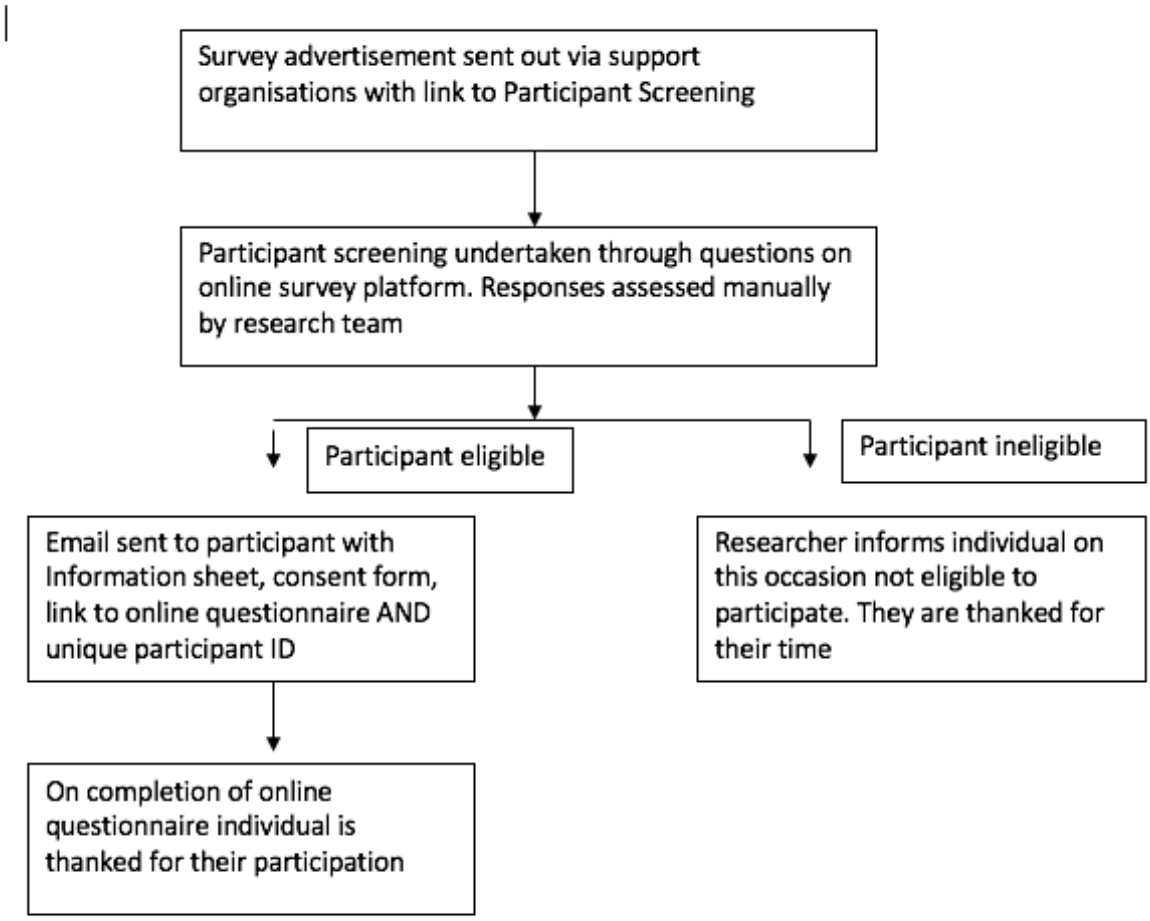
In addition to a self-reported diagnosis of ME/CFS by a medical practitioner, inclusion for the present study specified meeting the IOM clinical diagnostic criteria. This was established by applying algorithms supplied by the DSQv1 authors that uses symptom threshold scores (Jason and Sunnquist, 2018b).

3.3 Setting, recruitment and participants

3.3.1 Setting and recruitment

Using a cross-sectional design, participants were recruited online through advertisements on social media, support organisation websites and newsletters (Appendix 3) from November 2017 until May 2019. The author started participating in recruitment from November 2018 after an amendment to the ethics application. Recruitment followed an established pathway (Figure 2). Potential participants undertook the screening questionnaire (Appendix 4) via the online platform which was SurveyMonkey and these were assessed by the researchers. Clarification and assessment of complex cases, especially where the history of head trauma was unclear, were referred to the lead investigator. If potential participants were identified as eligible they were sent, via their nominated email address, a link which contained the participation information sheet (Appendix 5), online consent form (Appendix 6) study questionnaires and a unique identification number (see following appendices for the data pertaining to this thesis: Appendix 7 demographics; Appendix 8 DSQv1 and Appendix 9 SF-36). Those who were not eligible were sent an email with an explanation of why they did not meet study criteria and thanking them for their time. One reminder was sent to each eligible participant if they had not started or not completed the consent form and questionnaires and a thankyou email was sent to all participants who completed the full questionnaire (Appendix 10 for all email templates).

Figure 2. Study recruitment procedure



3.3.2 Inclusion and exclusion criteria

The study comprised adults (aged 18-65 years) who self-reported a diagnosis of ME/CFS by a suitably qualified Medical Practitioner. Exclusion criteria were a diagnosis of psychotic, bipolar or related disorder; a history of brain injury or other neurological illness; a history of alcohol or illicit drug abuse; pregnancy; an inability to speak or read English; and uncorrected visual difficulties such that a participant is unable to read and respond to questions. They were also excluded for the present study if they did not meet IOM clinical criteria. This was an additional step once participants had completed the full study.

3.3.3 Sample

As identified in the literature review, comparison of ME/CFS participants is difficult when each study utilises their own interpretation of the chosen criteria. The DSQv1 provides a standardised method of case ascertainment in these circumstances. In the present study, diagnosis according to the IOM clinical criteria was ascertained from participants responses to the DSQv1 and SF-36 via algorithms developed by Jason and Sunnquist (2018b).

3.4 Procedure for data entry and management

3.4.1 Data collection

As previously mentioned, the data collection tool was SurveyMonkey which was password protected. SurveyMonkey was used for both the initial screening questionnaire and for the full study. Data was extracted from SurveyMonkey to an excel spreadsheet in order to assess answers to the screening questionnaire. A separate participant tracker was established for those participants who met eligibility criteria in order to send reminders and a thankyou email if the survey was completed. The tracker was visible to the author and the lead investigator and was password protected.

3.4.2 Data entry

Data from SurveyMonkey was extracted to Excel and then to SPSS by a psychology honours student who also classified participants into the IOM criteria (Jason and Sunnquist, 2018b) and scored the SF-36 domains (Ware et al., 1994). Demographics, the DSQv1 symptom raw scores (frequency and severity on scales of 0-4), the combined DSQv1 domain scores (specified by the author) and SF-36 domain scores were supplied to the author. The original data is stored by the lead investigator.

3.5 Data analysis

Prior to summarising data and performing analysis, data was examined to assess assumptions for reporting of continuous variables and for correlation analysis. Descriptive statistics were obtained to describe the sample, summarise data and explore range of scores (mean, median, ranges and percentages); missing variables; and outliers. Normality of distribution was assessed with frequency histograms and Kolmogorov-Smirnov to guide descriptive and bivariate analysis. Correlation coefficients were interpreted as follows: .50 is strong; .40 is moderate to strong; .30 is moderate; .20 is small to moderate; .10 is weak (Cohen 1988). The criterion for statistical significance was set at $p < 0.05$. All data were analysed using IBM SPSS Statistics Software (version 25).

3.5.1 Ethical approval, informed consent and considerations

Ethical approval was received from the University of Tasmania Health & Medical Human Research Ethics Committee H0015630 and the study complied with the World Medical Association Declaration of Helsinki and the National Statement on Ethical Conduct in Human Research 2007. Data was deidentified for analysis. Participants could withdraw from participation or have their data removed at any point. As people with pwME are known to fatigue from cognitive tasks, participants were encouraged to have a family member or friend present when reading and signing the consent form however this was not a requirement of informed consent. Additionally, to allow for pacing of activity and reduction of fatigue, the questionnaire platform enabled the survey to be saved and completed over a number of sessions if required. Participants were able to opt to complete a hard-copy version of the consent form and study questionnaires, which was mailed to them with a stamped, return address envelope. There was no financial reimbursement.

3.6 Summary

This chapter detailed the methods used in the current study. This was a cross-sectional study which utilised two reliable and validated instruments for collecting self-reported symptom severity, everyday functional status and QoL. Data collection and management, participant eligibility and ethical considerations were discussed. The following chapter will detail the key findings of the study.

Chapter 4 Results

4.1 Overview

This chapter presents study results, including selection of the final sample and how the data was explored to guide descriptive and correlation analysis. A summary of some of the key findings is provided with each step of the analysis and a brief summary to conclude the chapter is provided.

4.2 Sample

4.2.1 Meeting case definition and final cohort for analysis

Out of 240 eligible participants who were sent links to the full study, two contacted the author by email to say they were not well enough to complete the study and they were thanked for their time and interest in the study. By May 2019 there were 191 who had completed the consent form and the required questionnaires for this study. Of these 34 did not meet IOM criteria hence they were excluded from further analysis. One participant was out of the age range hence they were also excluded from analysis. This participant may have incorrectly entered their age in the final study as they would have been excluded through initial screening if they had entered their age as over 65. This left 156 participants for the present study.

4.2.2 Missing data, out of range scores and outliers

There was missing data for relationship status (n=149). There was one missing value for "years since symptoms began" and two missing values for "yeas since diagnosis". These variables were not required for the main correlation analysis and so no methods for replacement of missing data were undertaken. There were no missing scores for the DSQv1 or SF-36 and scores for these domains were within range. SF-36 and DSQv1 domain scores were converted to z scores in SPSS to assess outliers and all scores were within the specified range of -3.29 and 3 indicating no outliers (Tabachnick & Fidell 2016).

4.2.3 Analysis assumptions

Cronbach's alphas were calculated for the DSQv1 domains, except for fatigue as it is a stand-alone symptom in the inventory. These indicated excellent internal consistency with values between 0.80 – 0.92. Histograms for continuous data were visually inspected and these were not normally distributed. Kolmogorov-Smirnov for the SF-36 domains were all significant indicating violation of assumption of normality (Pallant, 2016) and this was the case for the

DSQv1 domains of PEM, pain, autonomic and immune hence scores are reported as median and Interquartile Range (IQR). To assess if there were symptoms associated with worse functional outcomes the non-parametric Spearman's correlation coefficients (*rs*) were calculated between the DSQv1 domains and the SF-36 domains including the component summaries.

4.2.4 Sociodemographic Participant characteristics

The participant characteristics, including sociodemographic characteristics and ME/CFS related factors such as employment status are described in Table 2. The majority of respondents were female (88.5%) and highly educated. In all, 51 (32.7%) were in paid employment and 105 (67.3%) were not in paid employment. The median time that respondents had been experiencing symptoms was 11.21 years (IQR 4.79 – 22.83) and the median time that they had received a diagnosis was 5.64 years (IQR 2.54 - 12.5).

Table 2. Demographics

Characteristics	n	%
Sex		
Male	18	11.5
Female	138	88.5
Age, in years*	39.7 (12.3)	-
Educational level		
Highschool only	23	14.7
Technical/Diploma	45	28.8
First degree or higher	88	56.4
Language other than English		
Yes	15	9.6
No	141	90.4
Relationship status		
Never married	60	49.3
Married/defacto	73	49.3
Separated/divorced	15	10.1
Work reduced due to symptoms		
No/unsure	14	9.0
Yes	53	34.0
No longer work	89	57.1
Currently in Paid employment		
No	105	67.3
Yes	51	32.7
Years experienced symptoms+	11.2 1(4.879–22.83)	
Years with a diagnosis+	5.64 (2.54 - 12.5)	

*mean (Standard deviation) +median (interquartile range), counts and percentages may not reach 100% if there was were missing values

4.2.5 DSQv1 Symptoms

The full DSQv1 inventory is presented in Table 3 and indicates which symptoms make up the individual domains. Out of the eight DSQv1 symptom domains, the highest scores were for fatigue (75.00 IQR 75.00 – 87.50) followed by PEM (72.00 IQR 60.00 – 82.50) and then the neurocognitive domain (54.81 IQR 43.27 – 64.42).

Table 3. DSQv1 symptoms

Symptoms	n=156*+	
Fatigue	75.00	75.00-87.50
Post-exertional Malaise		
Dead heavy feeling after starting exercise	75.00	62.50-87.50
Next Day soreness	75.00	62.50-87.50
Mentally tired after slightest effort	62.50	50.00--87.50
Minimal exercise makes physically tired	75.00	62.50-87.50
Physically drained or sick	75.00	50.00-87.50
Sleep		
Feeling unrefreshed after you wake up	87.50	75.00-100.00
Need to nap daily	62.50	28.13-75.00
Problems falling asleep	50.00	37.50-75.00
Problems staying asleep	50.00	28.13-75.00
Waking up early	37.50	25.00-62.50
Sleep all day and stay awake all night	00.00	00.00-37.50
Pain		
Pain or aching in your muscles	68.75	50.00-87.50
Pain/stiffness/tenderness more one joint	62.50	40.63-87.50
Eye pain	25.00	00.00-50.00
Chest pain	25.00	00.00-37.50
bloating	43.75	25.00-62.50
Abdominal/stomach pain	37.50	25.00-50.00
Headaches	50.00	37.50-62.50
Neurocognitive		
Muscle twitches	62.50	37.50-75.00
Muscle weakness	50.00	25.00-75.00
Sensitivity to noise	50.00	37.50-75.00
Sensitivity to bright lights	50.00	25.00-75.00
Problems remembering things	62.50	50.00-75.00
Difficulty paying attention for a long time	75.00	62.50-87.50
Difficulty finding the right word to say	62.50	50.00-75.00
Difficulty understanding things	37.50	25.00-75.00
Only able to focus on one thing at a time	62.50	50.00-62.50
Unable to focus vision and/or attention	50.00	25.00-62.50
Loss of depth perception	25.00	00.00-37.50
Slowness of thought	50.00	37.50-75.00
Absent mindedness or forgetfulness	62.50	37.50-75.00
Autonomic		
Bladder problems	25.00	00.00-50.00

Irritable bowel problems	50.00	25.00-50.00
Nausea	25.00	25.00-75.00
Unsteady on feet like you might fall	37.50	25.00-50.00
Trouble catching your breath	37.50	25.00-50.00
Dizziness or fainting	37.50	25.00-37.50
Irregular heart beats	25.00	00.00-37.50
Neuroendocrine		
Losing or gaining weight without trying	50.00	06.25-75.00
No appetite	25.00	00.00-50.00
Sweating hands	00.00	00.00-25.00
Night sweats	25.00	12.50-50.00
Cold limbs arms legs hands	37.50	25.00-62.50
Feeling chills or shivers	25.00	00.00-50.00
Feeling hot or cold for no reason	50.00	25.00-62.50
Feeling like you have a high temperature	25.00	25.00-50.00
Feeling like you have a low temperature	25.00	00.00-37.50
Alcohol intolerance	50.00	00.00-87.50
Immune		
Sore throat	37.50	25.00-62.50
Tender/sore lymph nodes	37.50	25.00-62.50
Fever	18.75	00.00-25.00
Flu like illness	50.00	25.00-62.50
Smells/foods/chemicals feel sick	50.00	37.50-62.50

[a]Higher scores indicate higher severity of symptoms
+median (interquartile range)

Table 4 provides the domain scores for the DSQv1. Out of the eight DSQv1 symptom domains, the highest scores were for fatigue (75.00 IQR 75.00 – 87.50) followed by PEM (72.00 IQR 60.00 – 82.50) and then the neurocognitive domain (54.81 IQR 43.27 – 64.42).

Table 4. DSQv1 symptom domains

DSQ Domains	n=156*+	
Fatigue	75.00	75.00 – 87.50
PEM	72.50	60.00 – 82.50
Sleep	50.00	37.70 – 62.50
Pain	47.92	31.25 – 58.33
Neurocognitive	54.81	43.27 – 64.42
Autonomic	33.93	23.21 – 44.64
Neuroendocrine	32.50	25.00 – 41.25
Immune	40.00	25.00 – 50.00

*Higher scores indicate higher severity of symptoms
+median (interquartile range)

4.2.6 Everyday function and QoL

SF-36 scores are presented in Table 5. Out of the eight SF-36 subscales, the best preserved function was within the Role Emotional and Mental Health subscales. However, these subscales exhibited a large range of scores, especially in the Role Emotional sub scale (IQR 33 – 100) with 53.2% scoring 100 (the highest possible score). The worst score was in the Role Physical subscale, which asks questions regarding problems with work or other activities due to physical health problems, where 83.3% scored 0 (the lowest possible score). Three other domains also had a large proportion of 0 scores: Vitality (26.9%), Social Functioning (25.0%) and Role Emotional (22.4%,).

Table 5. SF-36 domain scores

SF-36	n=156[b+]	
Physical Function	30.00	20.00 – 40.00
Role Physical	00.00	00.00 - 00.00
Body Pain	32.00	22.00 – 52.00
General Health	20.00	10.00 – 30.00
Vitality	10.00	00.00 – 20.00
Social Functioning	25.00	03.25 – 50.00
Role Emotional	100.00	33.00 – 100.00
Mental Health	64.00	48.00 – 76.00
PCS	21.00	15.25 – 28.00
MHCS	39.00	27.25 – 48.00

[b]Higher scores indicate better function

+median (interquartile range)

4.2.7 Relationship between symptoms, everyday function and QoL

Spearman's correlations between DSQv1 symptom domains and SF-36 scores are presented in Table 6 with the domains that constitute the two summary scores grouped together.

Table 6. Spearman's Correlation matrix between SF-36 and DSQv1 domains

	Physical Health					Mental Health			Component summaries	
	Physical Function	Role Physical	Body Pain	General Health	Vitality	Social Functioning	Role Emotional	Mental Health	Physical Health	Mental Heath
Fatigue	-.441**	-.138	-.376**	-.353**	-.444**	-.414**	-.139	-.104	-.539**	-.380**
PEM	-.469**	-.168*	-.447**	-.292**	-.467**	-.526**	-.121	-.095	-.596**	-.401**
Sleep	-.238**	-.003	-.345**	-.183*	-.128	-.185*	-.172*	-.112	-.322**	-.227**
Pain	-.289**	-.137	-.606**	-.233**	-.155	-.141	-.074	-.027	-.506**	-.148
Neurocog	-.243**	-.237**	-.353**	-.182*	-.259**	-.207**	-.155	-.089	-.414**	-.238**
Autonomic	-.190*	-.187*	-.424**	-.182*	-.128	-.198*	-.134	-.013	-.375**	-.196**
Neuroenodo	-.155	-.127	-.316**	-.177*	-.113	-.243**	-.164*	-.123	-.309**	-.241**
Immune	-.208**	-.082	-.321**	-.237**	-.169*	-.128	-.076	-.008	-.347**	-.138

*Correlation is significant at the 0.05 level (2-tailed)
** Correlation is significant at the 0.01 level (2-tailed)

4.3 Summary

The current chapter presents the study results with a summary of some of the key findings at each step of the analysis. A correlation matrix is provided to answer the research question of "Which symptoms are associated with everyday functional impairment and reduced QoL in ME/CFS?". The findings from these results are discussed in the following chapter, with recommendations for practice and further research and a conclusion to the thesis.

Chapter 5 Discussion

5.1 Introduction

It is evident from the literature review and from the present study that pwME experience a number of symptoms, which may impact on their capacity to participate in a range of everyday activities and their QoL. Fatigue and PEM are often associated with reduced everyday function such as reduced employment and capacity to undertake ADL's. Additionally, autonomic related symptoms, such as orthostatic intolerance and pain also emerged in the literature review as areas that are currently under investigation for their prevalence, impact and relevance to clinical practice. This chapter will discuss the study findings, with reference to the study objectives and in the context of the broader literature on ME/CFS. Recommendations for further research and practice are provided with a focus on the implications symptoms and everyday functional limitations may have in the health care context based on the study findings. The health economic implications are also discussed. Strengths and limitations of the study are discussed and a conclusion to the thesis is also provided.

5.2 Key findings

The aim of this thesis was to explore the symptoms associated with everyday functional impairments and QoL in ME/CFS. The objectives being to 1) describe participants demographic characteristics and 2) explore symptoms (using the DSQv1) and their association with function and QoL (using the SF-36) with ME/CFS reported by a cohort of Australians to answer the research question:
"Which symptoms are associated with everyday functional impairment and reduced QoL in ME/CFS?". As such, the key findings were:

I. All symptom domains had a strong association with everyday functional impairment and reduced QoL due to physical problems. PEM, fatigue and pain had the strongest association overall.
II. The association between symptoms and mental health problems were weak.
III. More than half of the respondents indicated that they were no longer able to work.
IV. There was a large gap in time between when respondents first noticed symptoms and when they received a diagnosis.

5.3 Demographics

There was a large proportion of female respondents compared to males in the present study which is a common finding in the ME/CFS literature (IOM, 2015). As identified in the literature review, further population based studies are required to assess the true ratio of males to females with ME/CFS due to some recent discrepant findings using large scale data mining (Valdez et al. 2019). This has important implications for biological research as there is an increasing awareness of the influence of biological differences between males and females in disease processes (Regitz-Zagrosek 2012).

In the present study, a large proportion of participants had undertaken higher levels of education hence this cohort represents a reasonably well educated group of pwME. These levels of education are similar to a recent cross-sectional study in Australia with similar recruitment methods (Johnston et al., 2016) and a prospective/retrospective cohort study from clinical referrals in the United States (Unger et al., 2017). In comparison, samples drawn from a United Kingdom Biobank study (Kingdon et al., 2018) had a more even spread of educational attainment spanning from high school only through to higher education and post-graduate study. There may be a range of factors influencing the discrepancy in education levels across studies including country specific access to health care and wider recruitment methods for the biobank sample (Kingdon et al., 2018). It is unclear what the implications are for the high levels of education in the present study. Higher levels of education are associated with a range of health benefits in the general population including ability to access medical care and health literacy (Australian Institute of Health and Welfare (AIHW), 2018; Hahn & Truman, 2015). Despite the high levels of education and capacity to obtain a diagnosis, there was a reasonably large interval between time participants had been experiencing symptoms and time that they were diagnosed. The implications of a delayed diagnosis are unclear. One study suggested that a delay may increase risk of having a more severe course of illness (Pheby & Saffron 2009) however this has not been replicated in further studies. Certainly early changes in activity in response to energy restrictions would make sense given what is known about the effects ME/CFS has on aerobic metabolism (Stevens et al., 2018). Access to health care practitioners who can guide this would appear to be one benefit of an early diagnosis. An additional consequence may be that with a delay in diagnosis pwME may be presenting with secondary complications, making assessment and management more complex (Strassheim et al. 2017).

A reoccurring theme in the literature is that pwME often seek an explanation for their symptoms for many years before receiving a medical diagnosis of ME/CFS (IOM 2015). There is a paucity of data on population prevalence and diagnostic rates in Australia although a recent report from the Australian patient support group Emerge found 40% reported receiving a diagnosis within one to two years and fifteen percent took ten or more years (Emerge Australia, 2018). The literature review for this thesis identified that some of the barriers to making a diagnosis for health care workers were knowledge, confidence and attitudes regarding ME/CFS. A further structural barrier was identified in a community based epidemiological study in the United States (Jason et al. 1999) which found medically underserved minority groups, particularly Latino groups, had higher rates of ME/CFS but lower rates of a medical diagnosis. Although the Australian health care system is different to the United States, there still remain issues of equity of access to health care services. In particular, rurality, lower sociodemographic status and being Aboriginal or Torres Strait Islander are all associated with poorer health outcomes (Thomas, Wakerman & Humphreys 2015). It is not known what the Australian specific factors are that may lead to a delay in diagnosis of ME/CFS and this warrants further investigation.

In regards to employment, in the present study over half the participants were not in paid employment. These findings are consistent with previous research in Australia where Johnston et al. (2016) found just over half of the participants reported being unemployed. Similar rates of unemployment were found in a large cross-sectional study in Spain (Castro-Marrero et al., 2019). In the aforementioned cohort study in the United States with physician diagnosed ME/CFS (which does not specify criteria) a higher percentage, nearly three quarters, were unemployed (Unger et al., 2017) which may reflect severity of illness as participants were accessing specialist services. All three studies used different methods for diagnosis however rates of unemployment were consistently high. One implication of this this is that whilst there is outstanding questions regarding the specificity of diagnostic criteria, pwME experience high rates of unemployment across diagnostic criteria. Further examination of the present data could look for factors associated with work retention such as symptom severity, delay in diagnosis or length of illness. Future studies could examine the positive factors that enable retention of employment such as external support structures (the role of a carer, supportive work environment, active management of particular symptoms) of

which there is little existing published data beyond reports of clinician related experience (Carruthers et al. 2012).

5.4 Symptoms and their association with everyday function and QoL

In the present study a composite symptom severity score was used from a combined frequency and severity rating to estimate the overall perceived "impact" of a symptom. In the full 54 item symptom inventory, the highest scoring symptom was 'feeling unrefreshed when you wake up", followed by "fatigue" and then "dead heavy feeling after starting exercise". Often studies report prevalence of symptoms, for example when using the DSQv1 Jason et al. (2014) found that the most prevalent symptoms were fatigue, PEM, neurocognitive problems, and unrefreshing sleep. Similarly, fatigue, PEM and unrefreshing sleep were the most prevalent symptom in the study by Unger et al. (2017) that used the Centres for Disease control symptom inventory (Wagner et al. 2005). In an Australian study, the most prevalent symptoms were fatigue, PEM, cognitive difficulties, pain, sleep, light headedness and sensory problems (Johnston, Staines & Marshall-Gradisnik 2016). Although there is a difference in how symptoms are measured a similar symptom pattern is apparent in the present study with symptoms related to sleep, fatigue, PEM and neurocognitive problems being of high severity. This is also reflected in the domain scores with the highest domain score being fatigue, followed by PEM and then the neurocognitive domain. Although the present study did not include a measure of disease severity, the extreme limitations experienced by some participants can be seen in the Physical Function subscale which provides details concerning specific physical limitations. The lowest rating "limited a lot" were given for climbing one flight of stairs (21.1%); 28.8% walking one block (28.8%) and bathing or dressing yourself (9%).

5.4.1 PEM and fatigue

The PCS had moderate to strong negative correlations with all the DSQv1 domains. This was also the case for the MCS apart from pain and immune which were weak correlation coefficients and did not reach statistical significance. Overall the PCS had the strongest negative correlations with PEM, fatigue and pain. This is consistent with existing literature that identifies PEM as associated with functional impairment due to problems with energy production (McGregor et al., 2019, Stevens et al., 2018). Clarifying the symptom of PEM as opposed to other types of fatigue, including both physical and cognitive fatigue, in order to

both distinguish ME/CFS from other disease processes that include severe fatigue and to understand the complexity of fatigue within ME/CFS itself, is an ongoing pursuit in the biological and symptom measurement literature (McGregor et al. 2019). Recent developments to the DSQ PEM domain found asking participants PEM duration further distinguished those with ME/CFS from multiple sclerosis or post- polio Syndrome which are both associated with high levels of fatigue (Joseph et al., 2018). There is very limited literature on successful management approaches for fatigue or PEM apart from pacing (IOM, 2015). This highlights the need for clinician awareness of the complex nature of fatigue, and the importance of asking clarifying questions to discover if there are symptoms distinguishing fatigue and PEM so that appropriate activity management strategies can be implemented.

5.4.2 Pain

Although pain is not specified as an essential symptom for diagnosis according to the IOM criteria, it is identified as an important symptom to assess and manage (IOM, 2015). In the present study the severity of "pain or aching in your muscles" was reasonably high in the full DSQv1 symptom inventory. This is similar to a community participatory study exploring the DSQ symptoms which found participants identified muscle pain as one of the most common symptoms associated with PEM (Holtzman et al., 2019).

The DSQv1 pain domain and the SF-36 pain domain had the strongest negative correlation overall which may indicate that these two domains are measuring similar underlying constructs. It certainly indicates that for this group pain is often severe and is associated with reductions in everyday function. Pain also had moderate, statistically significant negative correlations with Physical Function and General Health. The correlations between pain and Role Emotional and Mental Health were very weak. This is surprising as pain is often associated with depression in ME/CFS (Strand et al. 2019).

5.4.3 Orthostatic intolerance and neurocognitive symptoms

Orthostatic intolerance, which is attributed to changes in autonomic function, is one optional symptom in the IOM criteria. The negative correlation between the autonomic symptom domain and SF-36 Pain and PCS were strong to moderate and although it reached statistical significance for the MCS it was a weak coefficient. The individual items that traditionally indicate orthostatic intolerance had reasonably low severity scores, these being: "unsteady on your feet like you might fall"; "trouble catching your breath"; "dizziness of fainting" and

"irregular heartbeats". However, the reasonably strong negative correlation with the PCS and Pain suggests the inclusion of orthostatic intolerance in the IOM criteria makes sense from at least a clinical perspective. Indeed, orthostatic intolerance is one symptom that is relatively amenable to both non-pharmacological and pharmacological interventions (Reynolds et al. 2014). Furthermore, there is evidence to suggest that the traditional measurements of orthostatic intolerance may not always reflect the pervasiveness of orthostatic related cardiac output in ME/CFS. A large study (n=150) found, even without traditional indicators of orthostatic intolerance on tilt table test such as a decrease in blood pressure or sustained rise in heart rate, participants had lower stroke volume and cardiac output (van Campen and Visser, 2018). These changes were not statistically different when stratified for participant severity, suggesting the changes were not due to deconditioning. There is also evidence that autonomic related cerebral blood flow changes may have a more pervasive effect on symptoms such as PEM, pain and neurocognitive function (Nijs & Ickmans 2013), hence, these symptoms may be interrelated and treating one may have an influence on the other.

5.4.4 Mental Health and subjective wellbeing

The MCS of the SF-36 includes Vitality and Social Functioning domains which could be due to either physical or mental health issues due to the way the questions are framed (McHorney, Ware & Raczek 1993). The Role Emotional and Mental Health sub domain scores were the highest scoring domains overall (indicating better function) and these had weak negative correlations with all DSQv1 symptom domains. However, Vitality was the second lowest scoring domain after Role Physical thus the association between symptoms and mental health function are unclear in the present study. It could be concluded that given the high scores in the two specific mental health domains that reductions in Social and Vitality were scored according to physical and not mental health reasons by participants. The Role Emotional sub scale did have a large number of participants scoring at the ceiling of the scale (53.2% scoring 100). This is a three item domain that asks for binary responses in regards to effect of emotional problems on regular activities: 1) cutting down activities 2) accomplishing less than participant would like and 3) being less careful in work or activities than usual (Ware, Keller & Kosinski 1994). Given the large proportion of respondents not working due to symptoms, rating high on this scale may simply be due to the scale not measuring relevant factors to this group of participants. The relatively high mental health scores may also reflect a response shift in this population whereby participants have adapted

to their illness and accepted their limitations (Reynolds, Brown & Jason 2009). Stratification by length of illness may be a further area of investigation.

There are some contradictory findings on the prevalence and role mental health issues play in ME/CFS. Mental health problems are not uncommon in chronic health conditions and may be both a consequence of illness burden, such as change in capacity, physiological changes in neurobiology (Katon 2011) or simply a co-diagnosis. Social isolation in particular is known to be associated with poor physical and mental health outcomes in chronic illness (Ubido & Scott-Samuel 2014). ME/CFS is known to lead to social isolation via restrictions in education, employment and capacity to participate in recreational activities (Anderson, Jason & Hlavaty 2014). A strong negative association between physical symptoms and social isolation is supported in the present study with PEM and fatigue having strong to moderate negative correlations with the Social domain. In a large (n=960) multi-site clinical epidemiology study (Bateman et al., 2015), that included physician diagnosis and assessment of ME/CFS, 60% of participants reported a co-morbid mental health issue and this contributed to illness severity over time. However, when assessing co-morbid multipliers of symptom frequency, severity and function in ME/CFS Natelson et al. (2019) found no significant difference between those with and without a co diagnosis of anxiety or depression. Many studies find a consistent preservation of SF-36 mental health scores in comparison to the low scores in the Physical, Role Physical and Vitality sub scales of the SF-36 (Jason et al. 2016; Kingdon et al. 2018; Unger et al. 2016) hence the present study is similar in this respect to other studies utilising the SF-36.

5.4.5 Restricted range of scores

It was surprising that there were mostly weak correlations between the DSQv1 symptom domains and the SF-36 Role Physical given the extreme limitations indicated by some participants in the Physical Function subscale. The DSQv1 neurocognitive domain had a small to moderate negative correlation but all other correlations were weak. Additionally, the large percentage of participants not in paid work would suggest significant role limitations hence one would expect a range of symptoms to have strong negative associations with this SF-36 sub scale. This domain had a high proportion of respondents at the floor of the scale. Hence the low correlations may be due to “restricted range” that will reduce correlation coefficients (Pallant 2016). As a cross sectional study these effects are not particularly

concerning, however they may indicate a limitation in the questionnaire to measure change over time in response to an intervention.

5.5 Strengths and limitations

5.5.1 Strengths

Strengths of this study include use of a ME/CFS specific symptom measurement tool that has strong psychometric properties and distinguishes between fatigue and PEM. It is known that a proportion of pwME have significant difficulties in accessing medical care or participating in research studies that require attendance at a facility (IOM, 2015). One potential benefit of online recruitment may be that some of these pwME may be able to participate in studies with a lower risk of exacerbating symptoms.

5.5.2 Limitations

The present study utilises correlation statistics that examines relationships between variables, however causation cannot be established. Further studies could examine the predictors of more severe fatigue, PEM and pain. Additionally, there are different dimensions to fatigue, such as cognitive fatigue (Karshikoff, Sundelin & Lasselin 2017), that may not be reflected using the DSQv1. Although the questionnaire includes a neurocognitive domain, it may require further validation with established fatigue questionnaires that examine different dimensions of fatigue such as the Fatigue Impact Scale (Fisk et al. 1994).

Given the literature discussed in this thesis, it is plausible that increased PEM will result in reductions in everyday functional capacity. However, it may also be the case that the SF-36 is measuring an underlying level of severity, which may in turn effect how easily PEM is induced. Furthermore, we did not ask if participants were pacing to reduce symptoms hence it is not possible to assess the effect of activity management strategies on severity of symptoms or function hence speculation about the efficacy of pacing cannot be made. Although symptoms such as PEM and functional impairments such as reduction in physical function and low employment rates are consistent with other studies, we do not know if this is a representative sample of the full ME/CFS population in Australia. The influence of education and health literacy as factors in participating in online studies stands out as one further area of enquiry. Additionally, education and health literacy as mediators of severity of illness in ME/CFS warrants further investigation as there is a paucity of data on this. Future studies

could examine distinct groups such as lower socio-economic groups, ethnic minorities, Aboriginal and Torres Straight Islanders or the over 65 age group.

5.5.3 Effect of co-morbidities

Although the present study excluded those with a serious psychiatric diagnosis or head injury, comorbidities such as autoimmune disease or non-psychotic related mental health issues were not factored into the current analysis as mediators of severity of symptoms or everyday function and QoL. Several studies have shown co-morbidities in ME/CFS may influence symptom severity or functional impairment and impact on work status (Bateman et al. 2015; Natelson et al. 2019). As previously mentioned, a delay in diagnosis may mean that pwME are presenting with complications, which may include co-morbidities, that may alter symptom profiles and further reduce everyday functional capacity and QoL.

5.6 Implications for research and practice

5.6.1 Symptom research and care

The NHMRC highlighted recently that there are no published referral pathways or guidelines to assist health care practitioners in appropriate management of ME/CFS within Australia (NHMRC, 2019). The present study highlights some of the symptoms that appear to have an impact on function and QoL for a group of pwME. This helps to inform health care practitioners on the symptoms to be particularly aware of when treating pwME. However, as can be seen from the DSQv1 symptom inventory, ME/CFS involves multiple symptoms hence it is important to understand the unique presentation and needs of each individual within the health care encounter. This could be achieved with an N of 1 study which may provide an avenue for examining the combined factors of living with a complex chronic illness such as symptom severity, functional capacity, structural supports, the lived environment and social connection. This may assist in understanding the factors that support and hinder access to healthcare (AIHW, 2018). The high severity rating of the symptom PEM, and the levels of everyday functional impairment in the present study suggests that the physical and cognitive resources required to access medical care may be impaired. A frequent theme in qualitative accounts is that pwME are seen on days they are well enough to be out visiting friends or attending medical appointments, however the consequent recovery time means they are at home and “invisible” at their worst times (Anderson, Jason & Hlavaty 2014). Health care providers may not be seeing pwME on their worst days. Furthermore,

evaluation of the impact of accessing health care services should be considered given PEM may be triggered with minimal activity. There is limited literature on the practicalities of accessing healthcare for pwME. For instance, how do health care workers need to adjust care plans and expectations? Are there particular considerations for pwME regarding recovery from major or minor surgical procedures or other health care interventions such as dentistry or physiotherapy and what supports can be implemented to facilitate better recovery? One possible avenue to reduce the burden of accessing care may be better access to health care in the home. Telehealth and home visiting services are currently very limited in the Australian health care system. Telehealth in particular is often funded for people living in rural areas (AIHW, 2018). Although rural living may be a further factor limiting access to healthcare, it can be assumed that those who are too ill to leave the house will have problems accessing healthcare regardless of proximity to services.

5.6.2 Economic and health service delivery implications

The present study confirms previous literature on the low employment rates in a segment of the ME/CFS population in Australia. This suggests there is a potential economic disadvantage for this population with extended economic burden on caregivers, lost productivity and possibly higher health care utilisation; however there is a paucity of published data on these factors within the Australian health care context. For example, in addition to the problems with obtaining a diagnosis, the potential economic impact raises concerns regarding unmet health care needs outside of Medicare's remit (physiotherapy, specialist services, non-Pharmaceutical Benefit Scheme medication). Are there food and housing security issues facing this population? Furthermore, potentially low rates of diagnosis may have implications for capturing health care service utilisation from large scale data sets such as hospital separation data although this may prove a useful starting point. The Australian Modification of the International Classification of Diseases (ICD-10-AM) is derived from the standardised classification system for epidemiology and health service utilisation maintained by the World Health Organisation (National Center for Health Statistics 2018). It is used in conjunction with Diagnostic Related Groups and the Australian Classification of Health Interventions to code all hospital separations and may provide one measure of health economic impact at the tertiary service delivery level.

5.7 Conclusion

The literature review highlighted biological discoveries that demonstrate a multi-system process that particularly relates to problems with exertion and recovery from exertion resulting in the symptom construct of PEM. PEM is specific to ME/CFS and is associated with everyday functional limitations however generic fatigue scales are inadequate to measure this unique symptom construct. The SF-36 was identified as the most appropriate function and QoL assessment tool to use in the larger study the thesis draws from due to its discriminant capacity to distinguish between those with and without ME/CFS on a number of sub scales and due to the use of the tool to quantify significant reduction in function for the DSQv1. This study found a strong association between PEM, fatigue and pain and the PCS of the SF 36 and lends further support for the symptoms of PEM, fatigue and pain as factors in everyday functional limitations which has implications for targeting symptom management and treatment options. Although pain is not included as a required symptom for a diagnosis of ME/CFS according to the IOM criteria, this study supports the importance of exploring the existence of pain in pwME in a clinical context in order to reduce symptom burden. Furthermore, although prevalence of orthostatic symptoms and the autonomic symptom domain did not have a particularly high scores recent literature suggests a more global autonomic dysregulation in ME/CFS that may be reflected in the fatigue, PEM and pain domain scores. There remain questions regarding the suitability of some sub scales in the SF-36 to capture meaningful variance in function. The floor effects in the Role Limitations due to physical problems and ceiling effects in Role Limitations due to emotional problems require further investigation. Furthermore, further validation of the DSQv1 in measuring different aspects of fatigue is warranted. The lack of clinical guidelines for ME/CFS in Australia are of particular concern given the high levels of everyday functional impairment identified in the present study and the health economic implications require further investigation in order to develop appropriate structural supports and for those living with ME/CFS in Australia.

Chapter 6 References

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Chapter 7 Appendices

Appendix 1 Literature review matrix

Study details Symptom sand function	**Study design**	**Rese arch question/s**	**notes**	**Measures/ sample**	**Results**	**Strengths/ weakness**
(Andersen, Permin & Albrecht 2008)	Longitudinal, 9 year follow up	Level of disability over time. Other studies have focused on percent remission	Had to meet Holmes and Fukuda criteria Self reported quality of life Nine outcome variables were constructed: work status, social impairment, hours per day sleeping and resting, cognitive disability, driving, neurological disturbances and allergies, depression/anxiety(D/A),sexual problems, and post-exertional malaise. Maintenance of a full or part time paid job defined normal work status. Normal functioning for other out come variables was defined as a score of less than 30% of maximum disability	At 9-year follow-up patients also responded to questions regarding health, fatigue, use of Health Care system, alcohol and exercise.	After 9 years QOL was the same, only mental health had improved Work highest disability score change to less strenuous; majority on disability or supported by family or spouse Social impairment: reduction in hobbies	Includes comprehensive list of outcome variables, Include PEM and distinguishes this from fatigue Excluded alternative diagnosis from statistical analysis. Small sample
(Pendergrast et al. 2016)	Cross section, quant using self report likert scales	Compare housebound vs non housebound		SF 36 and DSQ	25% housebound, sig	Sig diff all except role phys, mental health and role emotional. Lack of racial diversity But samples from 4 databases – heterogeneity across socio economic
(Anderson, Jason & Hlavaty 2014)	Qualitative natural history Longitudinal Recruited through epidemiological sample; Qualitative interviews	Nested qual study using recall to examine changes in life over time due to ME/CFS	Fukuda case definition. Recruited from a larger community epi study with physician diagnois and screening for exclusionary illness. Good population sample with spread of ethnicity, age, gender…more women represented Identified – occupational shift/reduction, global effect of stess (eg death of family member, being a carer), family system changes, Reductions in social and personal domains by 1/3 group Community attitudes – in particular negative medical response Physical symptomology – fatigue, PEM, memory and concentration, sleep disturbance and pain; relapsing nature of the illness Health changes – co morbid eg weight gain, auto immune diagnosis, gender specific issues – ME specific issues can woren when combined with other illnesses Balancing activity as coping mechanism	Community sample 19 people	Illness experience e impacts across multiple domains eg family, work, personal, mental, social Stress impacted on health, change in support structures	Small sample Helpful themes identified Strength – part of a large epi sample Risk of recall bias

(Schafer et al. 2015)	Cross section, quant – self report and actigraphy	Which self report q's reflect reduction in activity	Current work activity highest association with SF 36 scores	Actigraphy, sf 36, work status, DSQ		Not much looks at quantifying this criteria for diagnosis
(Anderson et al. 2012)	Meta synthesis of qualitative data	To review and synthesize findings across qualitative studies on Myalgic Encephalomye litis/chronic fatigue syndrome (ME/CFS).	First order constructs – experiences of people with ME/CFS – loss of identity, change in roles eg chidren taking on more responsibility, p 4 phases of illness and reconstruction of identity. Etiology – stress, infective, Qual lit supports the diagnostic criteria that describe substantial reductions across occupational, education, personal and or social domains. "In particular, people with ME/ CFS describe social and economic reductions, as well as personal losses and disruptions, in addition to the physical reductions experienced in everyday life"p loss of social roles Coping mechanisms – pacing, activity regulation, Symptom descriptions - Victim blaming, psychosomatic approach with unclear biomedical causes (p. 416) Gendered response Woodward, Broom, and Legge [23] found that obtaining a diagnosis was the single most helpful event in the search for social and medical legitimacy during the course of their illness. P4			Qual synthesis not as reducible as quant Varying diagnostic criteria Correlates patient experiences with data, helps to describe symptoms, identifies ethical and practical issues
(Kingdon et al. 2018)	compare the functional status and well-being of people with well-characterized ME/CFS with people with multiple sclerosis (PWMS), as well as	What is the difference in functional status and employment outcomes between ME/CFS, MS and healthy controls	Well characterised= Cfs can be similar or in this cohort, more disabling that MS Lower levels of employment maintenance – what are the factors? Lack of treatment, lack of support and understanding, level of functional impact higher?	Cross section UK ME/CFS Biobank to compare actual participant scores from the Medical Outcomes Survey Short Form-36 v2TM (SF-36v2TM) between groups	People with ME/CFS scored significantly lower than PWMS or HCs in almost all SF-36v2 furthermore, employment and income data are consistent with loss of functional status.	Difficult to generalize Self reported, some retrospective cross sectional design as may not represent their illness on more severe days

	healthy controls					
(Jason, LA et al. 2015)	Factor analysis of DSQ	Underlying factors to determine groups or subtypes	There may be underlying groupings that make more sense that may assist with creating more empiric diagnostic criteria	DSQ and SF 36	six factor solution,	Large numbers but many self reported symptoms. Use of validated self report measure, pain loaded across domains so not counted as a discreet variable
(Hardcastle et al. 2016)	Systematic review	Compare various scales	Severity scales may assist with distinguishing ME/CFS groups. Not uninform ally used so hard to compare studies			Severity scales may assist in identifying biological abnormalities.
(Strassheim et al. 2017)	Scoping literature review	Identify research relating to those severely and very severe	Case studies reported that in extreme presentations very severe CFS/ME individuals may be confined to bed, requiring reduced light and noise exposure. There are four categories of severity in the CFS/ME population: mild; moderate; severe; and very severe which are expanded on elsewhere and adopted by the National Institute for Health and Care Excellence	Narrative summary of results as discussed	Examines a seldom studied population	Unable to do full systematic given heterogeneity of literature
(McManimen et al. 2018)	Cross sectional, comparative, quantitative	Risk factors for SI in ME/CFS	Unsupportive social interactions, severe symptoms, stigma, depression interact as risk factors for suicidal ideation	DSQ, SF36, modified bec depression inventory, social stigma scale	Small percent who have SI without depression	Self report of symptoms First study to quantify these interactions
(Harvey et al. 2008)	Prospective birth cohort trial	Does prior psychiatric illness predispose to ME/CFS		Present state examination, Pinter personality inventory, psychiatric symptom	Yes, prior psychiatric illness does predispose	Controlled for current depression, prospective birth cohort population study (rare!) but poorly defined ME or CFS at last measurement so ? actually referring to ME/CFS

				frequency scale, various fatigue and fitness measures		
(Pheby & Saffron 2009)	Observational comparative study	What are the risk factors for severe ME/CFS		Barthel score for level of severity		
(Milrad et al. 2017)	Cross section Biological and self report data	What is the relationship between subjective reports of poor sleep, fatigue and cytokines in women	Poor sleep quality is associated with severity of fatigue, pro inflammatory cytokines Worse sleep qual greater fatigue severity and greater assoc btw fatigue and every day tasks	CDC CFS, Pittsburg sleep qual index, fatigue symptom inventory, plasma	Multi regression for associations	Does not establish etiology of sleep problems Studies linking pathology and symptoms seem rare Supports subjective reports of poor sleep quality with evidence of inflammation and effects on areas of functioning
(Haywood, Staniszewska & Chapman 2012)	Systematic review of patient reported outcome measures		Condition-specific, domain-specific and generic multi-item patient-reported outcome measures (PROMs) Importance of capturing patient perspective of impact f health conditions	Reliability, validity, responsiveness		Before DSQ SF36 only one with reasonable evidence There is no published evidence of completion rates, patient acceptability or feasibility of application for the remaining generic measures. Still floor effects.
Interventions						
(Collatz et al. 2016)	Systematic review	Pharmacological interventions	No universal pharma therapies can be recommended at this stage		Require better studies on better defined cohorts to reach a conclusion	Systematic review
(Castro-Marrero et al. 2017)	Literature review	What is the evidence for the different proposed therapies	Appears comprehensive, covers major areas of pharmacological and non pharmacological treatment	Evidence is weak, larger, better controlled	Individual care for each situation, keeping in mind evidence levels and	Not systematic however covers the major areas

				trials required in many areas	presentation of patient	
(Brown, Khorana & Jason 2011)	Data from a larger longitudinal study	Do patients who start treatment outside of their energy envelope improve in areas of fatigue, physical functioning, compared to those who start and stay within that envelope	Demonstrates tthat increased activity treatments may only be effective for a select group of patients Those who stayed within ee demonstrated improvements in fatigue and physical function No support found for a universal increase in activity for all those with ME/CFS Use of actigraphy data to have an objective element of measurement apart from self-reported data These findings do not provide support for treatment models of ME/CFS which suggest that increases in activity are necessary for patients with ME/CS to show improvement	The Physical Functioning subscale sf-36 Health Survey The Fatigue Severity Scale (was used to assess fatigue severity. -	those who were within their energy envelope before treatment showed more improvement in physical functioning and fatigue compared to those outside of their energy envelope.	GET styled treatment that pushes past symptoms not supported. Energy envelope more useful Large dropout as actigraphy identified as burdensome to collect for patients Small sample size
(Sunnquist & Jason 2018)	second-stage conditional process modeling (i.e., moderated mediation) to re-examine the behavioural pathway of the Vercoulen et al. (1998) mode	Does the Vercoulen model accurately represent those with ME/CFS	"This study represents the second attempt to replicate the Vercoulen et al. (1998) model; neither the Song and Jason (2005) nor the current study resulted in findings consistent with the original model. As this model provides the theoretical foundation for cognitive behavioral and graded exercise treatments for ME and CFS, these failed replication attempts support patient-expressed concerns about the appropriateness and efficacy of these treatments."		indicated that individuals did not reduce their activity level due to illness beliefs. Although activity level and impairment were significantly correlated, this correlation decreased as case definition stringency increased	Masters dissertation but published and peer reviewed
(Sharpe et al. 2015)	Follow up	investigate long-term outcomes (at least 2 years after randomization)	Use of oxford criteria		There was little evidence of differences in outcomes between the randomised	Authors maintain improvement - although concede muddied by inclusion and lack of control over other additional therapies

		originally included in the PACE trial.			treatment groups at long-term follow-up	included over the long term
(Jason, L. et al. 2009)	Comparison between those maintaining their ee and those outside of ee	Does maintaining activity within the EE improve function over time	Describes a number of scales - fatigue severity scale and short form 36 Interesting discussion of theories why extending beyond envelope causes an increase in symptoms		Staying within EE demonstrated improved function in physical function and fatigue severity	Small sample size
(Goudsmit et al. 2012)	Critical review	Pacing strategies	Pacing consistently identified as the preferred symptom management strategy amongst patients		Similar to above, number of studies have found pacing can reduce PEM	Critical evaluation of pros and cons, strengths and weaknesses
(Fluge et al. 2019)	Randomised controlled trial	B lymphocyte depletion with rituximab – does it help	Canadian Consensus Criteria cohort	Repeated measures fatigue scores, SF 36, adverse events, physical activity level	Both primary and secondary end points not achieved, in contrast to previous open label studies	RCT, very rare in this population
Diagnostic criteria				‘		
(Brurberg et al. 2014)	Systematic review	Case definitions, what populations are they representing	The prevalence estimates based on self-reports showed high variability, while clinically assessed estimates were more consistent, especially in the community samples.		Sensitivity and specificity is an issue for ALL criteria. Even more selective criteria may at times include psychopathology	Systematic, in depth analysis of criteria
(Carruthers et al. 2003)	Expert consensus	Case definition	Requires PEM, Canadian Consensus Criteria		Expert consensus	For clinical application, not empirically tested
(Jason et al. 2012)	Comparative, cross section, quant	Contrasting case definitions	Ramsey and CCC appear to select a more severely impacted subset of patients compared to the Fukuda critiera	Prequel to DSQ for symptoms, SF 36, psychiatric interview, medical	Higher hr in ME and ME/CFS vs Fukuda, longer trailmaking times in ME/CFS and ME vs Fukuda (cog test)	Medical diagnosis , excluded the very sick ie housebound or wheelchair bound

				assessment – cog testing and heart rate monitoring		
(Carruthers et al. 2011)	Expert consensus statement	To provide an agreed upon, specific to ME set of diagnostic criteria for both adults and paediatrics	To provide an agreed upon, specific to ME set of diagnostic criteria for both adults and paediatrics Post exertional, neuroimmune exhaustion cardinal symptom and essential to a diagnosis Pain and fatigue are bio alarm signals and must be treated seriously, they are a part of a global protection response		Expert consensus	Removed fatigue and six month requirement, much more complex,
(Institute of Medicine (IOM) 2015)	Major review of evidence and proposal of alternate criteria		Paradigm changing, emphasis on biological basis for ME/CFS New criteria does not include Pain or The SEID criteria leave symptoms such as pain, immunological manifestations such as raised lymph nodes or sore throat or gastrointestinal symptoms out of the diagnostic process entirely	Literature review, systematic review,	For easier clinical identification, now used on CDC website as criteria	Some criticism of the criteria in the literature ie (Jason, Leonard, McManimen, Stephanie, et al. 2015). SEID not as selective, broader range of severity captured than some, but more selective than Fukuda.
Epidemiology						
(Baraniuk 2017)	Population prevalence btw CDC and Oxford	To compare the selectivity of Oxford and Fukuda criteria in a U.S. population	Oxford criteria low threshold not particularly specific		Very little overlap between criteria, Oxford very broad	
(Johnston et al. 2013)	Meta analysis	Meta analysis to look at differences in prevalence according to method of assessment used	Heterogeneity of prevalence may in part be due to the variations in methods of assessment, in particular between self report and clinical assessment Helpful discussion p108 on gathering data, estimating prevalence and tools used	CDC criteria (Fukuda) Adults – self reporting vs clinical assessment	High variability with self reported More consistency with clinical reported. Pooled prev 0.87	ICC had not been out long – Fukuda most reliable for this study timeframe Use of Fukuda – lower or higher possible depending on criteria and place of sampling
(Reeves et al. 2007)	Epidemiology	To sample Georgian population for CFS		Random digit dialling to sample population	Prevalence 2.54%, used CDC criteria, higher prevalence than other studies	

				metro, urban rural Georgia, Follow up psych and medical		
(Jason et al. 1999)	Eidemiology, community	To sample the greater Chicago area for a community based sample establish prevalence	"There were no significant differences between in-individuals with CFS and controls with respect to marital status, educational attainment, or occupational status. However, individuals with CFS differed significantly from controls with respect to current employment status."p2136	Random digit dialling, follow up with psych and medical greater Chicago area	Prevalence 0.43% more selective ,but consistent with Reeves that disproportionate women, ethnic minority, lower edu and oc status	Realatively small sample size for epi – N=1031
Biological						
(Daniel, Annesley & Fisher 2019)	Review article		Despite these challenges, modern research demonstrates a tangible biomedical basis for the disorder across many body systems. This evidence is mostly comprised of disturbances to immunological and inflammatory pathways, autonomic and neurological dysfunction, abnormalities in muscle and mitochondrial function, shifts in metabolism, and gut physiology or gut microbiota disturbances. Homeostatic shift	Drawing from and critically reviewing biological evidence in different areas		Review article, not systematic
(van Campen & Visser 2018)			Decreases in stroke volume and cardiac output are not significantly different between mild, moderate, and severe ME/CFS patients. Therefore, this suggests that deconditioning does not explain the larger decrease in stroke volumes and cardiac output in ME/CFS patients compared to healthy controls.		Removed those with POTS or known orthostatic intolerance - ie included pts with otherwise normal ttt, diagnosis. Doppler carotid artery	Stroke volume index sig lower in ME/CFS on tilt but no sig changes within group stratified by severity Cardiac output lower ?reduced blood volume, reduced symp/parasymp tone ?dys reg autonomic nervous system
Nursing						
(Ryckeghem et al. 2017)	Qual interviews	Explore experience and expectations of GP's and patients for role of nurse practitioners	Deficiencies in guidance for patients "Coordinating care and timely communication with all relevant health care- givers and the patient is important. This study showed that GPs can only partially fulfil this coordinating role, partly because of difficulties in communication between the GP and the referral centre "	Semi structured interviews	Central role of a specialist nurse in coordinating care of a multidisciplinary approach to care and treatment	Rare nursing article that asked patients and GP's what would help them. Aus context may look different

(Chew-Graham et al. 2011)	Nested qual study in larger randomized PACE trial	Factors influencing participation in a nurse led home therapy of GET and CBT	Patient beliefs towards foundation of treatment influence engagement ie model of illness makes a difference High tensions when nurse and patient disagree		Conclude that GP's need to screen patients for underlying beliefs regarding symptoms before referring to such a service	Model based on "false illness beliefs" Some patients did find validation in not being alone with experience of symptoms. Tension in nurse/patient relationship when disagreement on causes of symptoms

Appendix 2 SF-36 and WHOQOL evaluation

ME/CFS specific studies		
	WHOQOL	SF -36
Quality of life in patients with CFS (Van Heck & De Vries 2002)	Yes, WHOQOLl 100 – not short form	
Expecting a good quality of life in health: assessing people with diverse diseases and conditions using the WHOQOL-BREF (Skevington & McCrate 2012)	WHOQOL-BREF discriminant validity.Compared with the SF-36, WHOQOL physical and psychological domains showed good concurrent validity, although social was weak.	
A comparison of health status in patients meeting alternative definitions for chronic fatigue syndrome/myalgic encephalomyelitis (Johnston et al. 2014)	WHO DAS Not directly compared but appear to corroborate eachother – ICC worse scores in all WHODAS domains compared to Fukuda	Yes – Australian based study – community based sample. ICC lower scores in all domains compared to Fukuda.
Assessment of activity limitations and participation restrictions with persons with chronic fatigue syndrome: a systematic review (Vergauwen et al. 2015)	WHOQOL 100 – can distinguish btw healthy controls and CFS	
A national cross-sectional survey of diagnosed sufferers of myalgic encephalomyelitis/chronic fatigue syndrome: pathways to diagnosis, changes in quality of life and service priorities (Comiskey & Larkan 2010)	WHOQOl- bref Cross section, delays in diagnosis, need for QOL, mean delay in diagnosis 4.7 years. Responsive to changes pre and post illness - retrospective	

Are Myalgic Encephalomyelitis and chronic fatigue syndrome different illnesses? A preliminary analysis (Jason et al. 2016)		sf-36 to measure levels of impairment across different diagnostic criteria – as identified by the DSQ -differences in severity depending on criteria so useful for breaking down types and areas of severity
Functional status in patients with CFS and other fatiguing illnesses and healthy controls (Buchwald et al. 1996)		Strongest correlation between physical functioning, role functioning, general health and body pain with CDC listed symptoms of flulike illness, fever, chills, sore throat, painful lymph nodes, weakness and myalgia. Emotional, social, mental health and vitality correlated poorly with signs and symptoms
Contrasting Chronic Fatigue Syndrome verses Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (Jason et al. 2013)		SF-36 can help distinguish between CFS and other illnesses but not within the different CFS constructs – older study without newer specific criteria
Integration of DNA methylation & health scores identifies subtypes in myalgic encephalomyelitis/chronic fatigue syndrome (de Vega et al. 2018)		Use De Paul and SF-36 to examine severity of symptoms, the SF-36 was an important component of correlating different subsets as identified by the DSQ into severity categories
Measuring substantial reductions in Functioning in patients with CFS (Jason et al. 2011)		Mental health component poor discriminant ability. Vitality, social functioning and Role Physical best discriminant ability. also evaluated past studies using controls and found that these three subscales still held . Davenport 2011 diverges with mental health having some predictive power for recovery fromPEM. Contains summary table of different SF36 results for a number of studies that report all 8 domains
Measuring substantial reductions in activity (Schafer et al. 2015)		Comparing current and past occupational status strong determinant of reduction in function. Correlation matrix: pos corr btw past occ and physical funct, vitality, and social funct. Current work pos with physical funct, bodily pain, vitality. Current household activities pos ass physical funct, role physical, vitality and social

Health Status in Patients with Chronic Fatigue Syndrome, General Population and Disease Comparison Groups (Komaroff et al. 1996)		Strong correlations with fevers, pharyngitis, muscle weakness, PEM and difficult thinking across the physical functioning domains – although R is not directly reported but the statistical significance p288. Use of older Holmes minor criteria.
Pain is associated with reduced quality of life and functional status in patients with Myalgic Encephalomyelitis and Chronic Fatigue Syndrome (Strand et al. 2019)		deficits on the physical functioning, bodily pain, general health functioning and social functional scales
The utility of patient reported outcome measures in people with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (Murdock et al. 2017)		Scores were reversed…but equal to floor effects found in role physical had ?consistency and floor effects problems
Functional Status and Well-Being in People with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Compared with People with Multiple Sclerosis and Healthy Controls (Kingdon et al. 2018)		Yes – good comparison data -MS and ME/CFS participants from a UK biobank. Group comparisons, not broken down by symptoms. Reports 8 domains.
Reliability and validity of Short Form 36 Version 2 to measure health perceptions in a sub-group of individuals with fatigue (Davenport et al 2011)		High concurrent validity sf36 and MIF 20 Floor effect in phys funct, role phys, vitality, mental health, social function, general health

Comparative study:

Measuring health-related quality of life in adults with chronic conditions in primary care settings (Hand 2016)

Quote: "The abbreviated World Health Organization Quality of Life Scale (WHOQOL-BREF), the 36-Item Short Form Health Survey (SF-36), and the Duke Health Profile were critiqued. All address physical, mental, and social domains, while the WHOQOL-BREF also addresses environment. Psychometric evidence supports use of the SF-36 and WHOQOL-BREF with this population. The SF-36 has the most evidence of responsiveness but has some floor and ceiling effects, while the WHOQOL-BREF does not appear to have floor or ceiling effects but has limited evidence of responsiveness. The WHOQOL-BREF has the highest proportion of individualized items which is a consideration in terms of burden on respondents."

SF-12

Acupuncture for chronic fatigue syndrome: a randomized, sham-controlled trial with single-blinded design (Ng & Yiu 2013). Only reference to SF-12. SF 12 requires more research in ME/CFS population before using as measurement of reduction in function.

Appendix 3 Study flyer

Impact of Fatigue in CFS

Call for Research Participants
Aged between 18 and 65 years

We are looking for volunteers with Chronic Fatigue Syndrome (CFS) or healthy individuals without CFS to take part in study investigating fatigue and its impact on everyday functioning.

As a participant, you will be asked to complete an **online survey**, which will ask you questions about your CFS, your experience with CFS and your everyday functioning. The questionnaire should take between 40 and 70 minutes to complete.

Participation in this study is entirely voluntary.

To volunteer or for further information please click on the link or use your QR scanner to complete the following screening questionnaire:

www.surveymonkey.com/r/F523WCY

Contact: Ms Kate Donnelly (kated@utas.edu.au)
OR Dr Cynthia Honan (cynthia.honan@utas.edu.au)
College of Health & Medicine, University of Tasmania

This study has been approved by the Tasmanian Health and Medical Human Research Ethics Committee [#H0015630].

Appendix 4 Screening questionnaire

Age: _____ (if aged under 18 years or over 65 years, individual is excluded)

Are you able to read and speak English? Y / N (if no, individual is excluded)

Do you have any uncorrected visual difficulties? Y / N

If yes, provide details?

_____

(Researcher to make decision about whether visual difficulties would prevent individual from validly completing tasks)

Do you have a diagnosis of a psychotic, bipolar or related disorder? _____

Do you have a history of brain injury or other neurological illness? _____

Do you have a history of alcohol or illicit drug abuse? _____

Are you pregnant? _____

(if yes to any of the above questions, individual is excluded)

Is your CFS diagnosis verifiable by a suitably qualified medical practitioner?

_____

Appendix 5 Participant Information

Discipline of Psychology, School of Medicine University of Tasmania

Participant Information Sheet

Fatigue in Multiple Sclerosis/Chronic Fatigue Syndrome

Introduction

You are invited to participate in a study that examines the nature of fatigue, factors that influence fatigue and how fatigue affects functional everyday outcomes. The research is being conducted by Dr Cynthia Honan and Dr Jane O'Brien. Ms Kate Donnelly will be assisting with the study in partial completion of an Honours in Nursing degree.

Purpose of the study

The purpose of this study is to investigate the relationship between subjectively experienced fatigue and functional outcomes (e.g., everyday social functioning, social participation, employment, quality of life) in people with multiple sclerosis (MS)/chronic fatigue syndrome (CFS) when compared to healthy individuals. Factors that may influence this relationship including sleep, illness severity, social support, diet and lifestyle, and cognitive skills, will also be investigated.

What does my participation involve?

If you wish to take part in this study, you will be asked some initial screening questions aimed at identifying whether you are suitable to participate. If you are deemed suitable, you will be emailed a unique participant number and a weblink to complete the full survey online. The survey will contain a series of questionnaires related to your: (1) general background; (2) MS/CFS symptoms (if you have MS/CFS); (3) diet; (4) alcohol use; (5) symptoms of depression; (6) experience of fatigue; (7) experience of daytime sleepiness; (8) sleep quality; (9) perceived thinking difficulties; (10) social functioning; (11) social support; and (12) quality of life and social participation. It is recommended that completion of the survey in the one sitting, although breaks can be taken when required. It is

estimated that the survey will take 40 to 70 minutes to complete. If you feel that you would like to complete the survey over a longer period of time, we can post the survey to you.

We will also ask you for permission to contact a family member or friend to complete a short survey about your social functioning and integration as a result of your illness or condition. A link will be provided at the end of the survey which can be emailed directly to your family or friend for completion.

Risks

There is minimal risk associated with your participation in this study. You may start to feel tired or fatigued while completing the questionnaires. Should this fatigue become excessive and you do not wish to continue, please advise the researcher and/or speak with your regular doctor about your fatigue. The questionnaires in this study also have the potential to cause distress due to their personal content relating to relationships with partners and family. If you are concerned about these questions and/or do feel distressed, please contact your regular doctor, Lifeline on 13 11 14 or MS Australia on 1800 042 138, or the researchers on 03 6324 3266.

Benefits

The current research is intended to improve our understanding of the nature of fatigue and the link that fatigue may have with various functional outcomes in MS/CFS. Whilst the benefits of participating in this research may not be of direct benefit to you, your participation will provide us with some invaluable information that will assist other people with MS/CFS, researchers, and clinicians to further understand in particular the types of fatigue-related factors which are most relevant in predicting everyday functioning. Such an understanding is important as it may lead to more effective rehabilitative treatment programs for those who experience difficulties with fatigue. Note that your individual results from the questionnaires will not be available.

Recompense to Participants

There will be no payment to individuals who participate in this study.

Consent

You are encouraged to discuss your participation with a family member, carer, or doctor prior to consenting to participate in this research. Where possible (or if asked by the researchers), please have a family member or carer present to witness your consent prior to completing the survey. Acknowledgement of the presence of a witness can be provided in the online survey link or by having your witness co-sign the included consent form (if receiving a hard-copy of the survey in the mail).

Voluntary ParticipationParticipation in this study is entirely voluntary. You do not have to take part in it. If you do take part, you can withdraw at any time without having to give a reason. Whatever your decision, please be assured that it will not affect your relationship with the researchers or any other medical personnel. Only the researchers named above will be aware of your participation or non-

participation. We recommend that you have a family member or friend present when agreeing to participate in this study.

Confidentiality

All the information collected from you for the study including all medical history and results will be treated confidentially, and only the researchers named above will have access to it. The results of this study may be presented at a conference or in a scientific publication, but individual participants will not be identifiable.

Further Information

When you have read this information, the researchers will be available to discuss it with you further and answer any questions you may have. If you would like to know more at any stage, please feel free to contact Kate Donnelly on kated@utas.edu.au or Dr Honan on cynthia.honan@utas.edu.au.

How do I find out the results of the study?

Results of the overall study can also be obtained by contacting Dr Honan on 03 6324 3266 or cynthia.honan@utas.edu.au.

Ethics Approval and Complaints

This study has been approved by the Tasmanian Health and Medical Human Research Ethics Committee. If you have concerns or complaints about the conduct of this study should contact the Executive Officer of the HREC (Tasmania) Network on (03) 6226 7479 or email human.ethics@utas.edu.au. The Executive Officer is the person nominated to receive complaints from research participants. You will need to quote H0015630. Any complaint you make will be treated in confidence and investigated.

Who do I contact if I wish to speak to someone about my mental health?

As aforementioned, a number of questions will be asked about psychological functioning and alcohol and other drug use. Whilst it is not anticipated that these questionnaires will cause distress, please do not hesitate to let the researcher know. If you are concerned about your mental health please contact your regular doctor, Lifeline on 13 11 14 or MS Australia on 1800 042 138, or the researchers.

Appendix 6 Consent form

Discipline of Psychology, School of Medicine University of Tasmania

PARTICIPANT CONSENT FORM

Fatigue in multiple sclerosis/chronic fatigue syndrome

I acknowledge that the nature, purpose and contemplated effects of the project so far as it affects me, have been fully explained to my satisfaction by the research worker and my consent is given voluntarily.

The details of the procedure proposed have also been explained to me, including the anticipated length of time it will take, the frequency with which the procedure will be performed, and an indication of any discomfort, which may be expected. I understand that my involvement means completing a survey (estimated time 40-70 min), although this may be longer if breaks are included.

I understand that there are the following risks or discomfort: fatigue due to questionnaire completion, and possible distress due to personal questioning about relationships.

Although I understand that the purpose of this study is to improve our understanding of fatigue in MS/chronic fatigue syndrome, leading to improved rehabilitation and treatment, it has also been explained that my involvement may not be of any benefit to me and that I will not be able to obtain my individual results from the researchers.

I have been notified that it is best to have a member of my family or a friend present while consenting to participate in this study.

I am informed that no information regarding any medical history will be divulged and the results of any tests involving me will not be published so as to reveal my identity.

I understand that my involvement in the project will not affect my relationship with the researchers or the University of Tasmania. I also understand that I am free to withdraw from the study at any time and have my data not be included in the study.

I understand that in agreeing to this electronic consent form, I am consenting to participate in the study. I am not giving up my legal right by agreeing to this consent form.

I understand that the trial will be conducted in accordance with the latest versions of the National Statement on Ethical Conduct in Human Research 2007 and applicable privacy laws.

I acknowledge that I have read the participant information sheet, have completed the screening questions, and

are deemed eligible to participate.	Yes/No
I agree to participate in this study.	Yes/No/Unsure (I would like to be contacted to discuss this further) IF Unsure, please enter your contact details (phone or email) _____

Please enter your participant number to begin: _____

Appendix 7 Demographics

Participant Survey Form

(CFS)

Please return completed form to:

Dr Cynthia Honan
Senior Lecturer and Clinical Neuropsychologist
Discipline of Psychology, School of Medicine, Faculty of Health
University of Tasmania
Locked Bag 1342, Launceston TAS 7250

If you have any questions or experience difficulty completing this survey, please do not hesitate to call Cynthia on 03 6324 3266 or by email: cynthia.honan@utas.edu.au

Participant ID: _____

Date Completed: _____

PART A: GENERAL BACKGROUND QUESTIONS

INSTRUCTIONS
The following set of questions asks you for general information about yourself. These questions are typical of research of this nature. Please answer every question. If you are not sure which answer to select, please choose the one answer that comes closest to describing you.

1. What is your date of birth? _____ (dd/mm/yy)

2. What is your gender? ☐ Male ☐ Other
☐ Female

3. What is your marital status? ☐ Never married
☐ Married/defacto
☐ Widowed
☐ Divorced/separated
☐ Other

4a. What is the *highest* level of secondary education you have achieved?

☐ Year 9 or below
☐ Year 10 (intermediate or school certificate)
☐ Year 11
☐ Year 12 / HSC (leaving certificate)

4b. Since school, what additional education have you received?

☐ I have not received any additional education
☐ TAFE certificate/diploma
☐ University or college degree
☐ Higher degree (postgraduate)

Please specify full-time years (or equivalent) of this education _____

5. To which ethnic group do you most strongly identify with? (*Please select one option only*)

☐ Australian
☐ Australian Aboriginal
☐ Torres Strait Islander
☐ Arab
☐ African
☐ Chinese
☐ English
☐ German
☐ Greek
☐ Indian/Hindustani
☐ Irish
☐ Italian
☐ Jewish
☐ Lebanese
☐ Malaysian
☐ Maori
☐ New Zealander
☐ Spanish
☐ Vietnamese
☐ Other (please specify _____)

6. Do you speak a language other than English at home? ☐ Yes ☐ No

If yes, which language do you speak at home? _____

7. Which of the following most accurately describes your current employment status? *(select one only)*

- ☐ Employed (full-time paid)
- ☐ Employed (part-time/casual paid)
- ☐ Unemployed
- ☐ Retired
- ☐ Student (full- or part-time)
- ☐ Regular volunteer work
- ☐ Permanently unable to work/ill
- ☐ Home duties

8. What is your current occupation (or most recent occupation if no longer working)?

_____

9. If you are *not currently working but have previously been in paid employment*, how long has it been since you were last employed?

Years _____ Months _____

Was this past employment on a full-time or part-time/casual basis?

- ☐ Full-time paid employment
- ☐ Part-time/casual paid employment

10. If you are *not currently working but have previously been in paid employment*, did you cease work because of your CFS?

- ☐ Yes
- ☐ No
- ☐ Unsure

11. By approximately how much has your work hours each week been reduced due to your CFS?

- ☐ I have not reduced my work hours
- ☐ There has been a small reduction (i.e. around 25%)
- ☐ There has been a moderate reduction (i.e. around 50%)
- ☐ There has been a large reduction (i.e. around 75%)
- ☐ I now no longer work at all (i.e. 100% reduction)
- ☐ Unsure

12. Have you been diagnosed with CFS/ME?

- ☐ Yes, from a medical doctor
- ☐ Yes, from an alternative practitioner
- ☐ No, but I have self-diagnosed

13. When were you diagnosed with CFS/ME? If you are unsure, please provide a close estimation (indicate month/year, e.g., June 2010).

_____

14. Have you always had persistent or recurring fatigue/energy problems, even back to your earliest memories as a child? (By persistent or recurring, we mean that the fatigue/energy problems are usually congoing and constant, but sometimes there are good and bad periods.)

- ☐ Yes
- ☐ No
- ☐ Not having a problem with fatigue/energy

15. How old were you when your problems with fatigue/energy began? (e.g., 21 years, 5 months)

_____

16. Over what period of time did your fatigue/energy-related illness, develop?

- ☐ Within 24 hours
- ☐ Over 1 week
- ☐ Over 1 month
- ☐ Over 2-6 months
- ☐ Over 7-12 months
- ☐ Over 1-2 years
- ☐ Over 3 or more years
- ☐ I am not ill

17. Please list any medications you are taking. Include prescription and over the counter medications and vitamins. Where possible indicate dose and frequency.

_____

_____

_____

_____

18. Do you currently take or have recently taken recreational or illicit drugs (e.g., cannabis or methamphetamine)?

- ☐ No
- ☐ Yes. Please provide details of drug used, frequency and quantity used each time.

_____

_____

19. Do you smoke tobacco?

- ☐ No
- ☐ Yes. Please specify how many cigarettes per day you smoke on average.

_____

20. Do you have a history of psychiatric illness (e.g., depression, anxiety, bipolar)?

- ☐ No
- ☐ Yes. Please specify this psychiatric illness with dates if possible.

_____

_____

21. Do you have a history of brain injury or neurological illness (e.g., epilepsy, encephalitis, Alzheimer's disease multiple sclerosis).

- ☐ No
- ☐ Yes. Please provide details of condition and diagnosis/injury date.

_____

_____

22. Are you pregnant?

- ☐ No
- ☐ Yes

23. Please list any other health-related conditions you currently have a diagnosis for (e.g., fibromyalgia, Type II diabetes, migraines, arthritis).

_____

_____

24. What is your current weight in kilograms (try to be as accurate as possible., e.g., 102kg) _____

25. What is your height in centimetres (try to be as accurate as possible e.g., 165cm) _____

Appendix 8 DePaul Symptom Questionnaire 54 symptom section

PART B: ABOUT YOUR CFS SYMPTOMS

For the following questions, we would like to know **how often you have had each symptom** and **how much each symptom has bothered you over the last 6 months**. For each symptom please circle **one number for frequency and one number for severity**. Please fill the chart out from left to right.

Symptoms	***Frequency:*** Throughout the **past 6 months, how often** have you had this symptom? For each symptom listed below, circle a number from: **0 = none of the time** **1 = a little of the time** **2 = about half the time** **3 = most of the time** **4 = all of the time**					***Severity:*** Throughout the **past 6 months, how much** has this symptom bothered you? For each symptom listed below, circle a number from: **0 = symptom not present** **1 = mild** **2 = moderate** **3 = severe** **4 = very severe**				
1) Fatigue/extreme tiredness	0	1	2	3	4	0	1	2	3	4
2) Dead, heavy feeling after starting to exercise	0	1	2	3	4	0	1	2	3	4
3) Next day soreness or fatigue after non-strenuous, everyday activities	0	1	2	3	4	0	1	2	3	4
4) Mentally tired after the slightest effort	0	1	2	3	4	0	1	2	3	4
5) Minimum exercise makes you physically tired	0	1	2	3	4	0	1	2	3	4
6) Physically drained or sick after mild activity	0	1	2	3	4	0	1	2	3	4
7) Feeling unrefreshed after you wake up in the morning	0	1	2	3	4	0	1	2	3	4
8) Need to nap daily	0	1	2	3	4	0	1	2	3	4
9) Problems falling asleep	0	1	2	3	4	0	1	2	3	4
10) Problems staying asleep	0	1	2	3	4	0	1	2	3	4
11) Waking up early in the morning (e.g. 3am)	0	1	2	3	4	0	1	2	3	4
12) Sleep all day and stay awake all night	0	1	2	3	4	0	1	2	3	4
13) Pain or aching in your muscles	0	1	2	3	4	0	1	2	3	4
14) Pain/stiffness/tenderness in more than one joint without swelling or redness	0	1	2	3	4	0	1	2	3	4
15) Eye pain	0	1	2	3	4	0	1	2	3	4

Symptoms	***Frequency:*** Throughout the **past 6 months**, **how often** have you had this symptom? For each symptom listed below, circle a number from: **0 = none of the time** **1 = a little of the time** **2 = about half the time** **3 = most of the time** **4 = all of the time**					***Severity:*** Throughout the **past 6 months**, **how much** has this symptom bothered you? For each symptom listed below, circle a number from: **0 = symptom not present** **1 = mild** **2 = moderate** **3= severe** **4 = very severe**				
16) Chest pain	0	1	2	3	4	0	1	2	3	4
17) Bloating	0	1	2	3	4	0	1	2	3	4
18) Abdomen/stomach pain	0	1	2	3	4	0	1	2	3	4
19) Headaches	0	1	2	3	4	0	1	2	3	4
20) Muscle twitches	0	1	2	3	4	0	1	2	3	4
21) Muscle weakness	0	1	2	3	4	0	1	2	3	4
22) Sensitivity to noise	0	1	2	3	4	0	1	2	3	4
23) Sensitivity to bright lights	0	1	2	3	4	0	1	2	3	4
24) Problems remembering things	0	1	2	3	4	0	1	2	3	4
25) Difficulty paying attention for a long period of time	0	1	2	3	4	0	1	2	3	4
26) Difficulty finding the right word to say or expressing thoughts	0	1	2	3	4	0	1	2	3	4
27) Difficulty understanding things	0	1	2	3	4	0	1	2	3	4
28) Only able to focus on one thing at a time	0	1	2	3	4	0	1	2	3	4
29) Unable to focus vision and/or attention	0	1	2	3	4	0	1	2	3	4
30) Loss of depth perception	0	1	2	3	4	0	1	2	3	4
31) Slowness of thought	0	1	2	3	4	0	1	2	3	4
32) Absent-mindedness or forgetfulness	0	1	2	3	4	0	1	2	3	4
33) Bladder problems	0	1	2	3	4	0	1	2	3	4
34) Irritable bowel problems	0	1	2	3	4	0	1	2	3	4

Symptoms	***Frequency:*** Throughout the **past 6 months**, how **often** have you had this symptom? For each symptom listed below, circle a number from: **0 = none of the time** **1 = a little of the time** **2 = about half the time** **3 = most of the time** **4 = all of the time**					***Severity:*** Throughout the **past 6 months**, how **much** has this symptom bothered you? For each symptom listed below, circle a number from: **0 = symptom not present** **1 = mild** **2 = moderate** **3= severe** **4 = very severe**				
35) Nausea	0	1	2	3	4	0	1	2	3	4
36) Feeling unsteady on your feet, like you might fall	0	1	2	3	4	0	1	2	3	4
37) Shortness of breath or trouble catching your breath	0	1	2	3	4	0	1	2	3	4
38) Dizziness or fainting	0	1	2	3	4	0	1	2	3	4
39) Irregular heart beats	0	1	2	3	4	0	1	2	3	4
40) Losing or gaining weight without trying	0	1	2	3	4	0	1	2	3	4
41) No appetite	0	1	2	3	4	0	1	2	3	4
42) Sweating hands	0	1	2	3	4	0	1	2	3	4
43) Night sweats	0	1	2	3	4	0	1	2	3	4
44) Cold limbs (e.g. arms, legs, hands)	0	1	2	3	4	0	1	2	3	4
45) Feeling chills or shivers	0	1	2	3	4	0	1	2	3	4
46) Feeling hot or cold for no reason	0	1	2	3	4	0	1	2	3	4
47) Feeling like you have a high temperature	0	1	2	3	4	0	1	2	3	4
48) Feeling like you have a low temperature	0	1	2	3	4	0	1	2	3	4
49) Alcohol intolerance	0	1	2	3	4	0	1	2	3	4
50) Sore throat	0	1	2	3	4	0	1	2	3	4
51) Tender/sore lymph nodes	0	1	2	3	4	0	1	2	3	4
52) Fever	0	1	2	3	4	0	1	2	3	4
53) Flu-like symptoms	0	1	2	3	4	0	1	2	3	4
54) Some smells, foods, medications, or chemicals make you feel sick	0	1	2	3	4	0	1	2	3	4

55. Since the onset of your problems with fatigue/energy, to what extent have your symptoms caused a reduction in your activity level? **Please indicate the percentage of reduction** (Note: 0% = No reduction at all, 50% = Reduced activities by half, 100% Activities no longer undertaken).

_____

56. Since your fatigue/energy-related illness began, do your headaches either happen more often, feel worse or more severe, or are they in a different place or spot?

- ☐ Yes
- ☐ No
- ☐ Not having a problem with fatigue/energy

57. Do you experience frequent viral infections with prolonged recovery periods?

- ☐ Yes
- ☐ No

57. Are you intolerant of extremes in temperatures (when it is extremely hot or cold)?

- ☐ Yes
- ☐ No

58. In the past 4 weeks, approximately how many hours per week have you spent doing:

Household related activities:	_____ (hours)
Social/Recreational related activities:	_____ (hours)
Family related activities:	_____ (hours)
Work related activities:	_____ (hours)

PART M: HEALTH STATUS

INSTRUCTIONS

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Answer every question by marking the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

1. In general, would you say your health is: ***(Please circle one)***

   Excellent 1
   Very good 2
   Good 3
   Fair 4
   Poor 5

2. **Compared to one year ago,** how would you rate your health in general now? ***(Please circle one)***

   Much better than one year ago 1
   Somewhat better now than one year ago 2
   About the same as one year ago 3
   Somewhat worse now than one year ago 4
   Much worse now than one year ago 5

3. The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

Activities	Yes, Limited A Lot	Yes, Limited A Little	No, Not Limited At All
Vigorous activities: running, lifting heavy objects, participating in strenuous sports	1	2	3
Moderate activities: moving a table, pushing a vacuum cleaner, bowling, playing golf	1	2	3
Lifting or carrying groceries	1	2	3
Climbing **several** flights of stairs	1	2	3
Climbing **one** flight of stairs	1	2	3
Bending, kneeling, or stooping	1	2	3
Walking **more than a mile**	1	2	3
Walking **several blocks**	1	2	3
Walking **one block**	1	2	3
Bathing or dressing yourself	1	2	3

4. During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities as a result of your **physical health**?

Problems	Yes	No
Cut down on the **amount of time** you spent on work or other activities	1	2
Accomplished less than you would like	1	2
Were **limited** in the **kind** of work or other activities	1	2
Had **difficulty** performing the work or other activities (For example, it took extra effort)	1	2

5. During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?

Problems	**Yes**	**No**
Cut down the **amount of time** you spent on work or other activities	1	2
Accomplished less than you would like	1	2
Didn't do work or other activities as **carefully** as usual	1	2

6. During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, neighbours, or groups? ***(Please circle one)***

Not at all 1
Slightly 2
Moderately 3
Quite a bit 4
Extremely 5

7. How much bodily pain have you had during the **past 4 weeks**?

None 1
Very mild 2
Mild 3
Moderate 4
Severe 5
Very Severe 6

8. During the **past 4 weeks**, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all 1
Slightly 2
Moderately 3
Quite a bit 4
Extremely 5

9. These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time **during the past 4 weeks**-

Questions	**All of the Time**	**Most of the Time**	**A Good Bit of the Time**	**Some of the Time**	**A Little of the Time**	**None of the Time**
Did you feel full of pep?	1	2	3	4	5	6
Have you been a nervous person?	1	2	3	4	5	6
Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
Have you felt calm and peaceful?	1	2	3	4	5	6
Did you have a lot of energy?	1	2	3	4	5	6
Have you felt down-hearted and blue?	1	2	3	4	5	6
Did you feel worn out?	1	2	3	4	5	6
Have you been a happy person?	1	2	3	4	5	6
Did you feel tired?	1	2	3	4	5	6

10. During the **past 4 weeks**, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time 1
Most of the time 2
Some of the time 3
A little of the time 4
None of the time 5

11. How **TRUE** or **FALSE** is each of following statements for you?

Statements	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
I seem to get sick a little easier than other people	1	2	3	4	5
I am as healthy as anybody I know	1	2	3	4	5
I expect my health to get worse	1	2	3	4	5
My health is excellent	1	2	3	4	5

Appendix 10 Email templates

Email to indicate eligibility and allocate participant number:

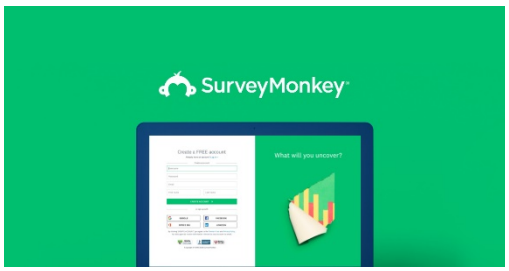
Thank you for expressing your interest in participating in the ***Impact of Fatigue in CFS (Myalgic Encephalomyelitis): Symptoms and Outcomes Study*** and for completing the screening questionnaire. Your responses indicate that you are eligible to participate in this study.

Your participant number is: 1234

You will need this number to enter the survey.

Please click on the following link to read the full participant information sheet, complete the consent form and complete the questionnaire. This questionnaire should take between 40 and 70 minutes to complete. If you wish to take a break, you can close the survey and return via this link. https://www.surveymonkey.com/r/VF73779

There is also a brief 5-to-10 minute questionnaire that we are hoping someone who knows you well can complete. This forms part of our extended investigation of how fatigue may affect social functioning. Participation in this is optional.www.surveymonkey.com/r/FBHCMLP



Impact of Fatigue in Chronic Fatigue Syndrome (Myalgic Encephalomyelitis) (Symptoms and Outcomes Study) Informant Questionnaire

www.surveymonkey.com

Many thanks for participating in this study. Your participation is invaluable to us and very much appreciated. If you have any questions or concerns, please do not hesitate to contact me on 0437468758 or kated@utas.edu.au. You can also contact the principal investigator Dr Cynthia Honan on 03 6324 3266 or cynthia.honan@utas.edu.au.

Kind regards,

Kate Donnelly, RN
Honours in Nursing candidate
Nursing | School of Health Sciences
College of Health and Medicine
University of Tasmania
Tel: +61 (0)4 ....
Email: kated@utas.edu.au
utas.edu.au/health

Email to indicate not eligible

Dear

Thank you for expressing your interest in participating in the ***Impact of Fatigue in CFS (Myalgic Encephalomyelitis): Symptoms and Outcomes Study*** and completing the screening questionnaire.

Your responses indicate that you are not eligible to participate in this study. In particular, you have indicated that you ……..

We appreciate that you have taken the time to undertake the screening process and should we undertake further studies, we would welcome your interest in participation. Please do not hesitate to email me if you would like to discuss this further.
You can also contact the principal investigator Dr Cynthia Honan on 03 6324 3266 orcynthia.honan@utas.edu.au.

Kind regards

Kate Donnelly, RN
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Nursing | School of Health Sciences
College of Health and Medicine
University of Tasmania
Tel: +61 (0)4 ....
Email: kated@utas.edu.au
utas.edu.au/health

Reminder email:

Dear

A short time ago you indicated your interest in completing our survey 'Impact of Fatigue in Chronic Fatigue Syndrome (Myalgic Encephalomyelitis): Symptoms and Outcomes Study. This important study aims to expand our current understanding of the manner in which CFS/ME might affect every day functioning. We would still very much value your input into this study if you are able to spare the time. You can enter the survey via the link in the original email.

Kind regards,

Kate Donnelly, RN
Honours in Nursing candidate
Nursing | School of Health Sciences
College of Health and Medicine
University of Tasmania
Tel: +61 (0)4 ....
Email: kated@utas.edu.au
utas.edu.au/health

Thankyou emial for completed surveys:

Dear

We wish to thank you for completing the surey by the University of ***Tasmania Impact of Fatigue in Chronic Fatigue Syndrome (Myalgic Encephalomyelitis): Symptoms and Outcomes Study.***

The research is intended to improve our understanding of CFS/ME Symptomology and the link this may have with everyday functional outcomes in CFS/ME. Your participation will provide us with some invaluable information that will assist other people with CFS/ME, researhcers, clinicians in the future.

Your participation is invaluable to us and very much appreciated. If you have any questions or concerns, plese do not hesitate to contact me on 0437468758 or kated@utas.edu.au. You can also contact the principle investigator Dr Cynthia Honan on 03 243266 or cynthia.honan@utas.edu.au

Kind regards

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